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STUDIES OF THE HUMAN COLON: I. VARIATIONS IN CONCENTRATION OF LYSOZYME WITH LIFE SITUATION AND EMOTIONAL STATE. By WILLIAM J. GRACE, M.D., PAUL H. SETON, A.B., STEWART WOLF, M.D. and HAROLD G. WOLFF, M.D. 241

TREATMENT OF POLIOMYELITIS INVOLVING THE RESPIRATORY SYSTEM. By HAROLD E. WEST, M.D. and ALBERT G. BOWER, M.D. 252

THE EFFECT OF THERAPEUTIC DOSES OF ASPIRIN ON THE ACID-BASE BALANCE OF THE BLOOD IN NORMAL ADULTS. By HERBERT R. FARBER, M.D., MARVIN J. YIENGST, B.S. and NATHAN W. SHOCK, Ph.D. 256

STUDY OF FIXED TISSUE SECTIONS OF STERNAL BONE MARROW OBTAINED BY NEEDLE ASPIRATION. III. METASTATIC CARCINOMA IN STERNAL BONE MARROW. By AUSTIN S. WEISBERGER, M.D. and ROBERT W. HEINLE, M.D. 263

THE BLOOD PICTURE IN LEPROSY. By SADIE KIANG, M.D. and G. H. CHOA, M.D. . . 269

EFFECT OF HESPERIDIN METHYL CHALCONE (VITAMIN P) ON DIABETIC RETINOPATHY. By FRANKLIN B. PECK, M.D. and MORTIMER MANN, M.D. 277

THE ELECTROCARDIOGRAM IN MYOCARDIAL INFARCTION: ITS VALUE AS A DIAGNOSTIC AID IN 130 AUTOPSIED CASES. By ROBERT B. FAILEY, JR., M.D. 283

NEGATIVE RESULTS OF TOCOPHEROL THERAPY IN CARDIOVASCULAR DISEASE. By CHARLES K. DONEGAN, M.D., ADDISON L. MESSER, M.D. and EDWARD S. ORGAIN, M.D. 294

ELECTROCARDIOGRAPHIC CHANGES IN ACUTE GONOCOCCAL ARTHRITIS AND MYOCARDITIS SIMULATING ACUTE RHEUMATIC POLYARTHRITIS. By EDWARD SHAPIRO, M.D., MAURICE L. LIPKIS, M.D., JULIUS KAHN, M.D. and JOHN B. HEID, M.D. . 300

AMYLOID HEART DISEASE. By JOSEPH BALLINGER, M.D. 308

THE PNEUMONIA OF MEASLES. By LOUIS WEINSTEIN, M.D. and WILLIAM FRANKLIN, M.D. 314

PROGRESS OF MEDICAL SCIENCE:

PREVENTIVE MEDICINE AND EPIDEMIOLOGY. By JOHN E. GORDON, M.D. . . 325

PATHOLOGY AND BACTERIOLOGY. By DONALD S. FLEMING, M.D. . . . 345

PROCEEDINGS OF THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA . . . 355

Contents continued on adv. page 10

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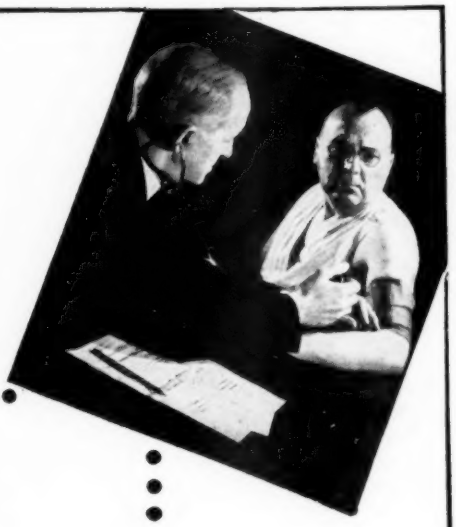

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THE AMERICAN JOURNAL
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MARCH 1949

ORIGINAL ARTICLES

STUDIES OF THE HUMAN COLON: I. VARIATIONS IN CONCENTRATION OF LYSOZYME WITH LIFE SITUATION AND EMOTIONAL STATE*†

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Lysozyme, a bacteriolytic and mucolytic enzyme, was first described by Fleming in 1922[2], when he was studying the anti-bacterial properties of tears. Since then the enzyme has been shown to be present not only in human tears[2,7] but also in nasal mucus[12], gastric juice, the secretions of the large and small intestines[3,4,7] and human milk[1]. All pathologic transudates and exudates contain large amounts[13]. The richest source of this lytic enzyme is egg white of hen's eggs. Further studies[5,9,11] on this substance have shown it to be a basic protein or polypeptide containing about 16% nitrogen and 2 or 3% sulphur. It is of small molecular size, having a diameter of less than 30 millimicrons. It is soluble and heat stable in acid solution, but insoluble and heat labile in alkaline solutions.

Recent studies on the substrate of this enzyme by Karl Meyer and his associates[6,7] have shown that the enzyme depolymerizes certain high molecular weight amino carbohydrates which they have isolated from susceptible organisms (Micrococcus Lysodeitkicus or Sarcina Lutea). However, the search for the substrate of lysozyme in various organs of the body has thus far been fruitless.

Lysozyme concentrations can be

* Presented in part at the 1948 meeting of the American Federation for Clinical Research, May 4th, 1948, and at the New York Academy of Medicine (Clinical Research Meeting), April 29th, 1948.

† Aided by grants from the Lester N. Hofheimer Foundation.

measured by determining the rate of clearing of opaque suspensions of the susceptible organisms or by determining the rate of depolymerization of the substrate isolated from the susceptible organism by the viscosimetric method of Meyer[7].

Meyer has further shown that the lysozyme concentrations are very high in the gastric juice of patients with peptic ulcer and in the stools of patients with chronic ulcerative colitis[3,4]. He has demonstrated that lysozyme will digest mucus and postulates that the destruction of the protective coating of the bowel exposes the underlying mucosa to the action of noxious agents of the intestine such as hydrochloric acid or the indigenous bacterial flora. These postulates he has substantiated in part by feeding lysozyme to dogs and thus producing acute ulceration of the upper gastro-intestinal tract[8].

Because of these findings, it seemed profitable to explore variations in lysozyme concentration in the stools of human subjects under a variety of circumstances and life situations.

Method. All tests were done according to the viscosimetric method of Meyer.

The specimens of wet stool were extracted with 0.1 normal hydrochloric acid (2 gm. of stool per 10 cc. of 0.1 normal HCl) within a few hours after their passage and stored in an ice box at 4°C. Just prior to carrying out the assay, appropriate dilutions of the extract were made with normal saline so that half viscosity would be reached within 30 minutes.

As far as possible, all specimens from the same subject were assayed on the same day, using the same substrate.

The substrates used had a relative viscosity close to 3.5, and the one sample which was standardized by comparison with a sample of purified lysozyme obtained from Dr. Karl Meyer was accurate within 2%, the approximate range of error of the method at this level of viscosity. At viscosity readings higher than 50, the method is accurate within 3-4%.

Stool specimens, both random and 24-hour samples, were analyzed. They were obtained from subjects with a variety of disease states as well as from normal subjects. In the case of two subjects, secretions obtained directly from the surface of the exposed intestinal mucosa were studied.

In addition, day to day determinations were carried out on specimens from a series of patients with ulcerative colitis and mucous colitis, as well as from a series of normal subjects. On each subject, a diary was kept which contained data relating to events in the life situation, emotions, attitudes and feeling states. The day to day observations were then correlated with symptomatology referable to the colon and also with other bodily complaints and the general level of well being.

Finally, the effect of the application of lysozyme to the human colon was studied.

Results. The range of lysozyme concentration observed among all the groups of subjects are summarized in Table 1.

Normal Subjects. Healthy individuals without complaints were regarded as normal subjects. Among these individuals, lysozyme concentrations were uniformly low during times of relative calm and security. Figures ranged from 0.3 to 1.7 units per gram of wet stool. In a subject with acute congestive heart failure, the lysozyme concentration was likewise quite low (1.2).

Two subjects who were studied daily were normal except that they were prone to develop diarrhea in circumstances of anxiety and apprehension. In these subjects, as detailed below, there occurred a rise in lysozyme concentration which was small, but definite, and was noted during the time of anxiety and apprehension and the associated diarrhea. In a third subject, studied daily, there was noted a rise in lysozyme during a period of anger and resentment, unassociated with any change in bowel function.

Case 1. One of these subjects was a 26 year old white male who 2 years previously had had a mild episode of ulcerative colitis from which he made a complete symptomatic recovery. Roentgen-ray and sigmoidoscopic examination were unremarkable. During periods of relative security and relaxation, stool concentrations of lysozyme were found to range between 0.3 and 0.8. During a period of anticipation of returning to visit

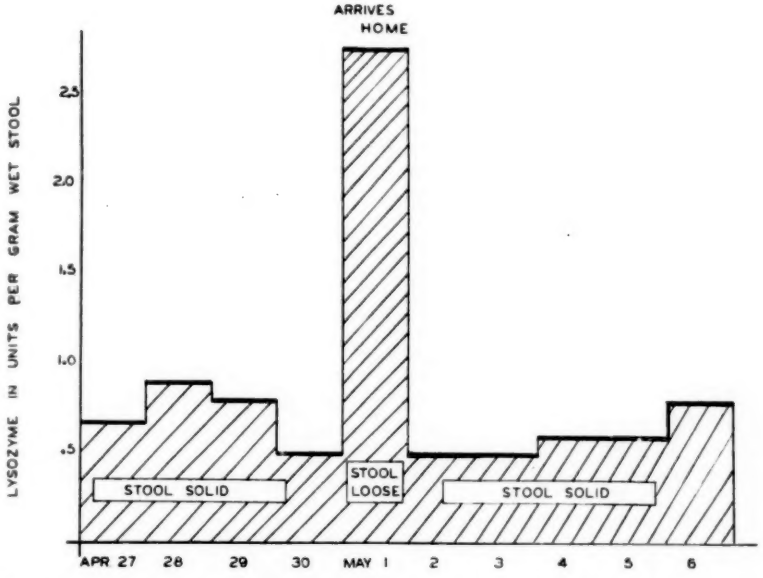

FIG. 1.—Transitory marked rise in lysozyme concentration in the stool associated with anxiety and conflict (Case 1). All assays of the stool specimens were carried out on the same substrate on the same day.

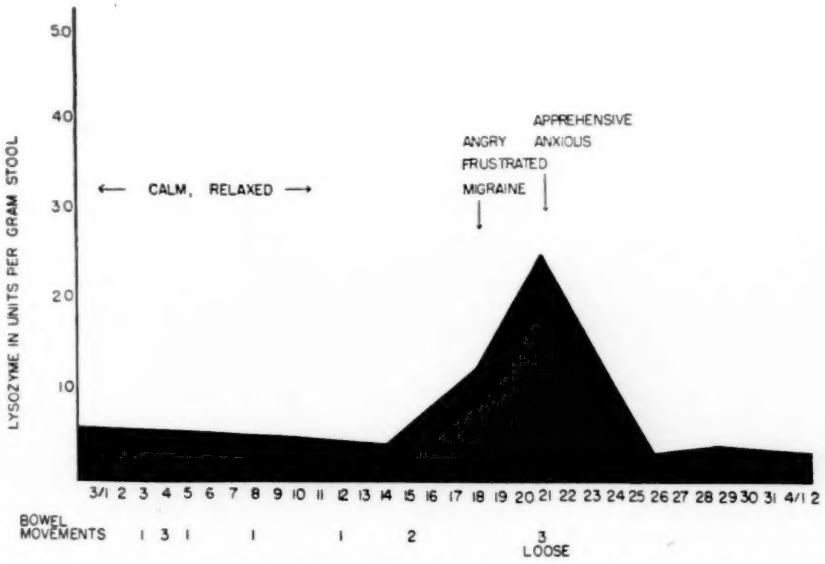
LYSOZYME IN UNITS PER GRAM STOOL
50
40
30
20
10
APPREHENSIVE
ANGRY ANXIOUS
FRUSTRATED
MIGRAINE
← CALM, RELAXED →
3/1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 4/1 2
BOWEL MOVEMENTS 1 3 1 1 1 2 3 LOOSE

FIG. 2.—Abrupt rise of lysozyme concentration associated with loose stools in a normal male (Case 2). All determinations were performed on the same substrate.

his parents and presenting to them a young woman whom he hoped to marry, he developed diarrhea and a concomitant rise in lysozyme to 2.8. Later, when he was comparatively secure and relaxed, the values fell again to 0.5 (See Figure 1).

CASE 2. Another subject was a 32 year old married physician, also inclined to develop diarrhea in situations productive of anxiety, insecurity, guilt and resentment.

On days of relative calm, security and self-assurance, the lysozyme stool content was low (0.4 to 0.6 units per gm.). During a period of increasing anger, hostility and resentment over a series of frustrating episodes associated with his experiments which precipitated a migraine headache, the lysozyme concentrations gradually rose to 1.2 units per gm. On the day following an acute episode of apprehension and anxiety over the presentation of an ill-prepared case at a conference, the concentration of stool lysozyme rose to 2.5 units. On subsequent days of calm and relaxation, the lysozyme concentration again fell to and remained at low levels (See Figure 2).

CASE 3. A 54 year old white male had undergone 13 years previous to our studies a "double barrel" colostomy because of a rectal stricture secondary to lymphogranuloma venerum. Shortly after the operation there occurred and persisted a large prolapse of descending and sigmoid colon through the stoma. He was otherwise healthy, however, and at the time of study his colonic mucous membrane was of essentially normal appearance. Specimens of mucus were obtained directly from the exposed bowel.

Usually he was relatively relaxed and self-assured. At such times the values for lysozyme concentration of the bowel secretions were low (0.1 units per gm.). Following an episode of questioning, however, when he mistakenly thought he was being looked upon as a homosexual, he reacted violently, with anger and bitter resentment persisting for 2 days. During this period, the lysozyme concentration rose to 10.8 units per gm. Subsequently, but only with vigorous reassurance, he became calm and relaxed again, and the lysozyme fell to lower figures (2.8 and 0.4 units per gm.). See Figure 3.

Comment. From these data, it would appear that in normal subjects there may occur a rise in colonic lysozyme concentrations in response to situational threats productive of anxiety and apprehension and during periods of anger, hostility, and resentment. The increase in lysozyme concentration in these subjects was not of great magnitude, however; neither was it sustained over a period of days. Being thus of minor degree and transitory, it was probably of little importance to the welfare of the individual.

(2) PATIENTS WITH ULCERATIVE COLITIS. In a series of 12 patients with ulcerative colitis in a state of remission, with minimal symptoms and enjoying feelings of relative relaxation and security, the stool lysozyme concentrations were low (0.7 to 1.6 units per gm.). In 4 patients with ulcerative colitis whose symptoms were mild, stool concentrations varied from 13-25 units per gm. In 3 subjects with ulcerative colitis whose symptoms were moderately severe, concentrations of stool lysozyme varied from 40 to 100 units.

In subjects with ulcerative colitis in whom day to day observations were made, lysozyme concentration was low during remissions which coincided with periods of relative self-assurance and security. During exacerbations, however, usually marked by situations provocative of unexpressed anger, hostility, and resentment, there occurred sharp rises in stool lysozyme. In fact a sustained, marked elevation of lysozyme concentration usually presaged a period of bloody diarrhea, as illustrated by the following protocol.

CASE 4. A 36 year old graduate nurse had had bloody diarrhea for 4 years. Repeated sigmoidoscopic examination, Roentgen-ray and stool examinations for pathogenic organisms supported the diagnosis of ulcerative colitis. The patient was a rigid, immature, insecure, obsessive, compulsive personality, almost completely unable to express either hostile or warm feelings. Marital life had been characterized by persistent turmoil, chiefly over difficulties with her in-laws and differences with her husband. In Fig. 4 are summarized the findings in her case.

The initial low figures were obtained during times of relative calm, security, relaxation, and smooth environment. Just before the first rise, a control specimen showed a value of 2.5 units per gm. The following afternoon

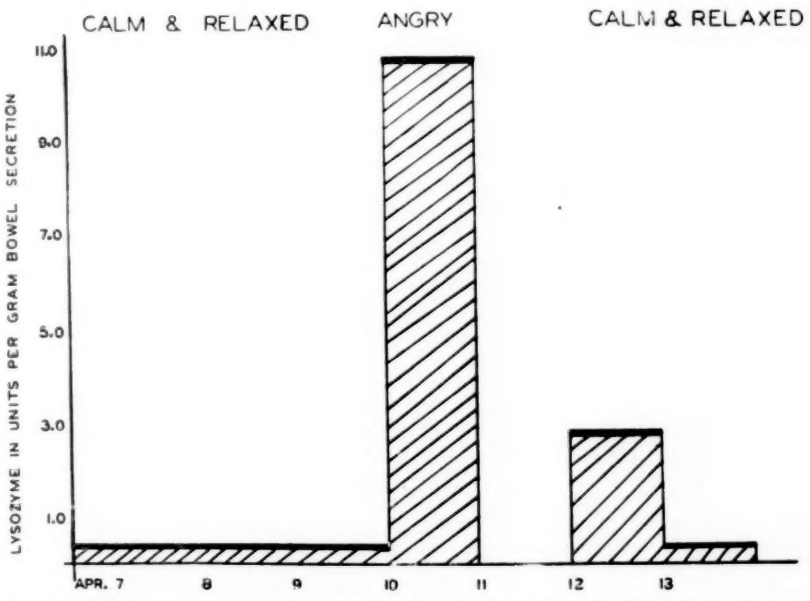

FIG. 3.—Variations of lysozyme concentration in the colonic secretions of a fistulous subject (Case 3) with marked increase during anger and resentment. All specimens were assayed using the same substrate.

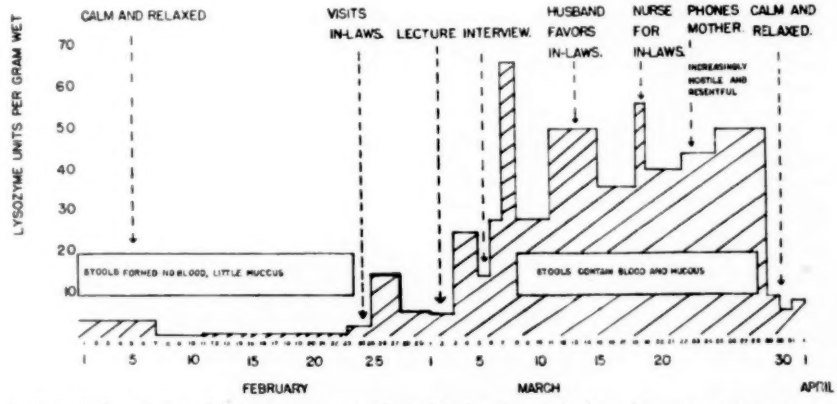

FIG. 4.—Case 4. Correlation of lysozyme concentration with situation, attitude and symptomatology in a subject with chronic ulcerative colitis. All determinations performed on the same sample of substrate.

was spent visiting her in-laws, whom she hates and blames for most of her difficulties, but toward whom she is unable to express verbally or act out her resentment. By the following day the lysozyme concentration had risen to 14 units per gm. Six days later, the value fell to 5 units per gm. The patient spent March 1st attending a lecture on psychoanalytic interpretations of aggression. She knew her husband would object to this, and she felt considerable guilt over it. She hurried home to prepare his dinner, and faced him that evening with mixed feelings of guilt, hostility, and resentment. The following day, the lysozyme concentration rose to 25 units per gm. There was no exacerbation of symptoms on this occasion.

During the next few days she gradually became more calm and concomitantly the lysozyme concentration fell to 14. On March 4th she had an interview with a member of our staff whom she thought was a psychiatrist. The interview upset her considerably, as she felt that he could easily "see through" her defenses. She was quite disturbed and angry, and she felt humiliated. She rushed

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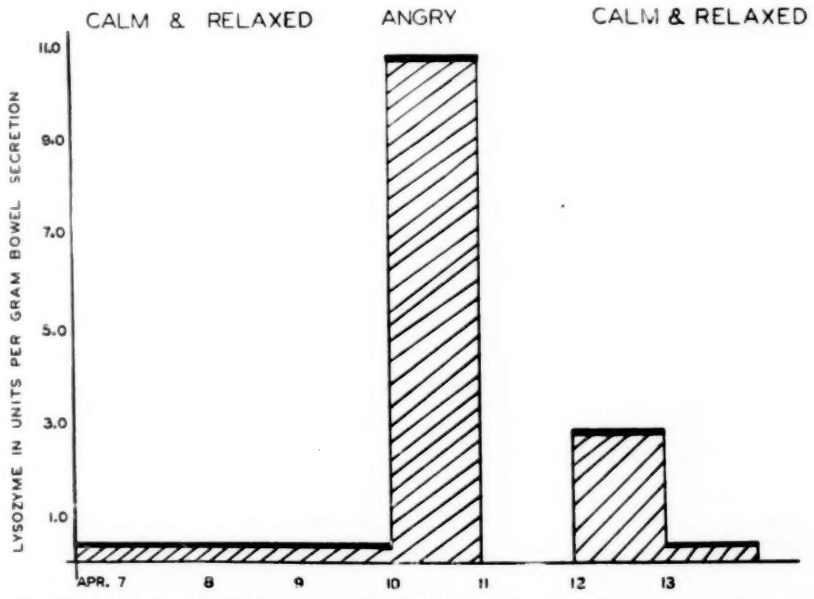

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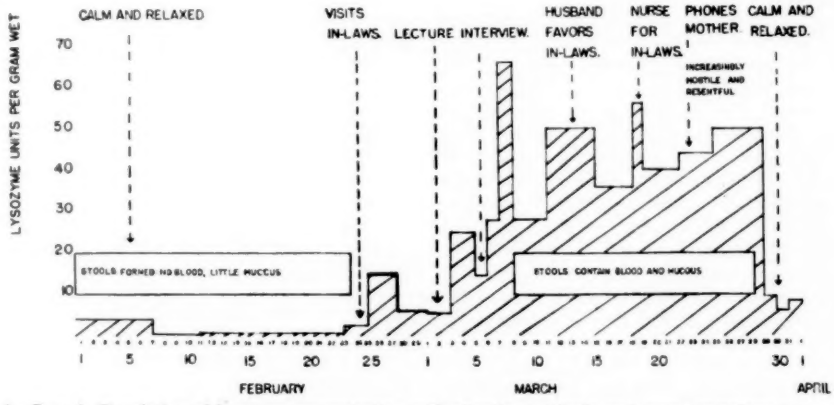

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blindly from the office, and was half-way home on the train before she could compose herself. The following day the lysozyme had risen to 66 units. She was having moderately severe abdominal cramps on this and subsequent days, and the stools were grossly bloody. By the 8th of March the patient had somewhat regained her composure, and the lysozyme was 28 units. During the period of March 10 to 15 the patient's husband began to make plans to provide for a vacation for his parents, and the plans were culminated by the patient, her husband and in-laws spending a week-end looking for a hotel for the in-laws. During this period, she was becoming more and more bitter, angry and resentful, but kept her feelings to herself. The crowning blow was the husband's announcement that he and the patient could not afford to take a vacation and that furthermore, he was planning to provide a practical nurse for the parents. Recalling that when she was severely ill and hospitalized with ulcerative colitis the husband had never proposed providing her a nurse, she became violently angry, resentful, and hostile and the lysozyme, which had fallen to 36, rose again to 57 units. At this time, she was having only one bowel movement every 2 or 3 days, but these stools were accompanied by considerable mucus and blood. The next week-end the patient placed a long overdue telephone call to her parents in Montreal with mixed feelings of guilt and anxiety. During the conversation, her husband stood over her with a stop-watch and sharply reminded her when her time was up. At this she again became angry, resentful, and hostile. She took no aggressive action, however; maintained a cool exterior but inwardly seethed with anger for the next few days. The lysozyme concentration in her stools, which had begun to decrease, rose again during the remainder of the week to 40, 44, and 50 units per gm., and constipation became more pronounced. However, the following week, after unburdening herself of some of these hostile feelings to her doctor, she gradually regained relative serenity and her bowel movements became regular and daily, and the blood disappeared. By this time lysozyme had fallen to low levels of 9, 6, 8, and 7 units per gm.

CASE 5. A 26-year old white male automobile mechanic had had ulcerative colitis for 6 years. Shortly after the onset of symptoms he was treated surgically by cecostomy, and later, 4 years before he was seen at New York Hospital, by ileostomy. Two years after the ileostomy a fistula developed through the old cecostomy wound. A loop of ascending colon evaginated through this defect and lay exposed on the surface of the abdomen. Specimens of mucus secretion from the surface of this loop were examined daily for lysozyme and correlated with the amount of secretion, the contractile state of the bowel, feeling states, attitudes, general behavior, and life situation. During times of relaxation and security, lysozyme values were low, ranging from 14 to 35 units per gm. On days of hostility, anger and resentment, lysozyme concentration in the secretions was markedly elevated (80 to 100 units per gm.). At such times it was often possible by reassurance, and by allowing the patient to express freely his feelings, to effect a significant fall in lysozyme concentration. There did not appear to be a direct relationship between the amount of mucus secretion and the concentration of lysozyme in the mucus. At times they were both increased, both decreased or one increased and the other decreased. In Figure 5, lysozyme values are correlated with variations in attitudes and emotional reaction.

It is apparent that situations associated with relative calm and security correspond with relatively low lysozyme titers in the neighborhood of 15 to 25 units per gm. of secretion. Situations associated with anger, hostility, guilt, and resentment, on the other hand, were associated with increased lysozyme production of 80 to 100. One such humiliating episode occurred when the patient, an extremely fastidious person, was allowed to sleep late, then brusquely awakened and sent to the laboratory without affording him time to wash, shave, or change his dressing. He characteristically took pride in having a clean and neat dressing. When he arrived at the laboratory, he was angry, irritable, and very resentful about being placed in such an embarrassing position. His lysozyme concentration was accordingly elevated to 80 (March 4th). On another day the patient was to be sigmoidoscoped (March 2), a procedure which he dreaded, because of unpleasant past experiences. The prospect irritated him and he felt anxious and apprehensive over it. Associated with this reaction the lysozyme was 67. On another occasion, the patient arrived at the laboratory fuming with anger. He had just received news that his sister-in-law was about to move back into his house. He objected to this violently, and felt that his brother was "putting something over on him" while he was in the hospital. A specimen obtained at that time contained 80 units of lysozyme (March 13). A few days later, he was visited by his sister-in-law. In order to avoid unpleasantness in the ward, he was "nice" to her, although he was seething inwardly. On this occasion, the lysozyme was 100 (March 15). These high levels con-

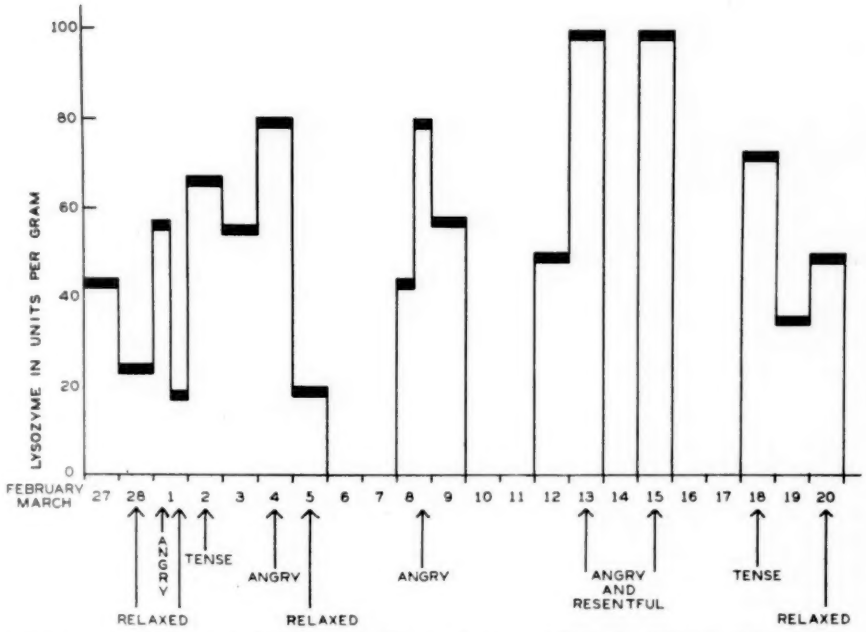

FIG. 5.—Case 5. Correlation of feeling states with day to day variations in lysozyme concentration in the secretions removed from the surface of the exposed bowel.

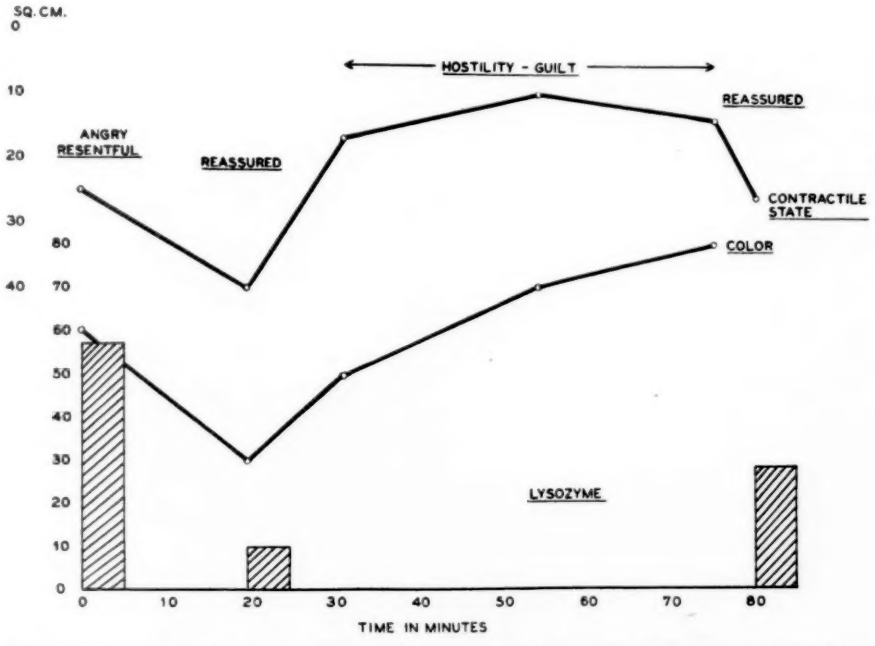

FIG. 6.—Case 5. Variations in lysozyme concentrations in the secretion of the exposed bowel in the interview situation on a day when the patient was angry, resentful and hostile.

trast strikingly with the comparatively low values of 19, 20, and 36 when the patient was relatively content, secure, cheerful, and relaxed.

Figure 6 shows the variation in the lysozyme concentrations during the following experimental situation, which included an interview, at first reassuring, and then traumatic:

On arriving at the laboratory, the patient was irritable, angry, and hostile because three doctors had come to his bed, removed his dressing, and, after merely examining his colon, had walked away without speaking to him. He said that he felt like a "freak", and was going to "sign out" of the hospital. Lysozyme concentration in the secretion following this episode was 57 units per gm.

After about 30 minutes of reassuring discussion and ventilation, he felt more relaxed, and within a few minutes the lysozyme concentration had dropped to 10 units. The discussion was abruptly switched to certain events in the patient's life about which he was in great conflict. He spoke of them with poorly concealed feelings of hostility, resentment, and guilt. At the end of the interview, the lysozyme concentration had risen to 33.

In contrast to this ready variability in lysozyme concentration was the relatively fixed situation on another day. On this day, the patient was relatively secure, calm, and relaxed. The interviewer was unsuccessful in his attempt to elicit any evidence of feelings of guilt, hostility, or resentment, even though topics usually sensitive were discussed. Rather did the patient seem reassured by the opportunity to unburden himself of his conflicts. Lysozyme concentration fell from an initial level of 25 to a level of 14 at the end of the interview.

A third interview situation is represented by Figure 7.

The patient arrived at the laboratory quite cheerful and in good spirits. During the interview, previously concealed topics of significant conflict were uncovered. Discussion of them was fraught with embarrassment and discomfort on the part of the patient as well as with considerable feeling of resentment and hostility. The initial lysozyme value of 19 gave way to 33 at the end of the interview.

(3) Lysozyme in Mucous Colitis: In 6 patients with mild mucous colitis, both those with diarrhea and those with constipation, lysozyme concentration was low (0.4 to 1.5).

In one subject with moderately severe constipation and mucous colitis, lysozyme concentration was in the neighborhood of 25 during times of anger, hostility, resentment. During periods of relative security, lysozyme in the stool fell to lower levels. One subject with mucous colitis displayed fairly marked changes in lysozyme concentration which corresponded to changes in symptomatology and life situation.

Case 6. A 36 year old negro chorus girl, in a setting of realization of her inability to compete with younger women, frustration at being unprepared to do any other type of work, and bitter resentment about her lot in life, developed watery diarrhea with cramps and the passage of mucus. A specimen taken when she was first seen in the clinic, at which time she was complaining chiefly of constipation, and had developed a fissure-in-ano, showed a relatively high lysozyme titer of 27 units per gm. At a later date, following several interviews in which she was encouraged to express freely her feelings and was given strong reassurance and moral support, the lysozyme fell to 14 units.

Later, she was hospitalized on the gynecological service because of irregular menses. After 3 days in the hospital being prepared for operation her menses began, so she was discharged without operation. She resented the loss of 4 days of work and felt that nothing had been accomplished. She did not express her hostile feelings, but concomitantly stool specimens contained lysozyme in a concentration of 25 units per gm.

At a later period, during a time of considerably more peace of mind consequent upon obtaining a new job and being paid by the union for her lost time, the lysozyme concentration fell to 8.5 units per gm. (See Fig. 8).

(4) Lysozyme in Carcinoma of the Colon: The possibility that ulceration itself might provoke an elaboration of lysozyme was further tested by analyzing the stools of a subject with an ulcerated carcinoma of the colon. Lysozyme concentration was, however, persistently low (3.2).

(5) Relevance of Lysozyme Concentration to Tissue Damage: Attempts to assess the effects of lysozyme applied to the intact colonic mucosa were made in the case of the subject described above (Case 3), who was healthy except for a colostomy through

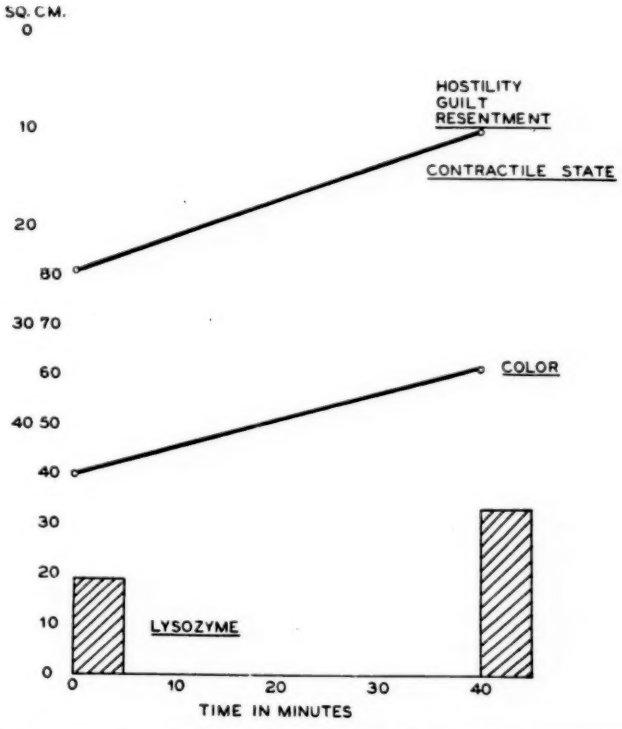

FIG. 7.—Case 5. Hyperemia, hypermotility of the colon and rise in lysozyme concentration associated with feelings of hostility, guilt and resentment. Color values were obtained by direct comparison under standard lighting to a Tallqvist hemoglobin scale standardized by the method of Munsell. The figures representing contractile state were obtained from direct measurement of the length and width of the exposed loop of bowel.

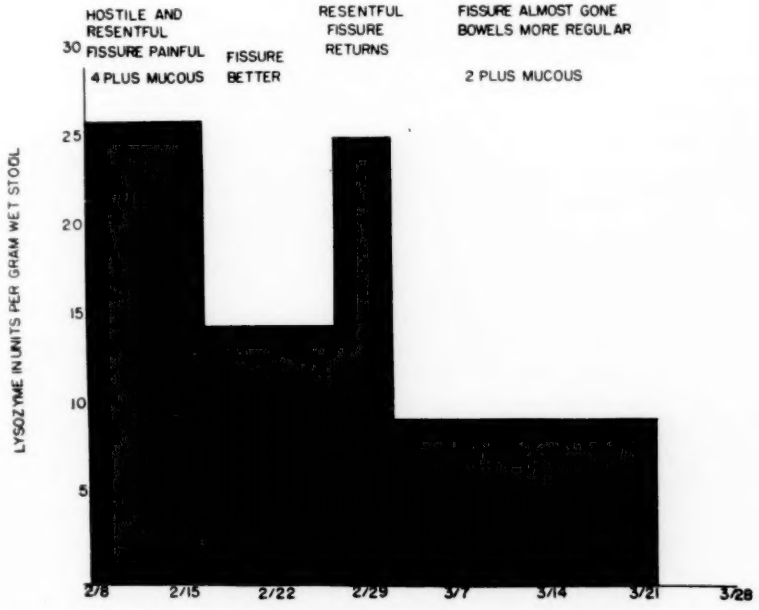

FIG. 8.—Case 6. Correlation of feeling state with lysozyme concentration and mucus in the stool of a subject with severe mucus colitis. All specimens determined on the same day and on the same substrate.

which had herniated a large segment of sigmoid colon.

Human tears containing lysozyme in a concentration of 600 units per cc. were applied to the surface of the bowel on small cotton pledgets and allowed to remain in place for 24 hours. At the end of this time, in 3 of 4 such experiments, a small, sharply circumscribed area of inflammation and edema was noted at the point of application. Control applications of normal saline, boiled tears and dry cotton failed each time to produce any lesion.

Comment: The fact that unboiled tears are capable of bringing about injury to the mucous membrane of the normal human colon, while boiled tears and saline fail to do so, suggests that the lysozyme may be responsible for damaging the colonic mucosa, or, by removing the protective mucus coating, for exposing the mucosa to injury from trauma or infection. This finding in humans is in keeping with the data of Meyer in which intestinal ulcers were produced in animals by feeding lysozyme. An analogous situation had been produced in cats by Rappaport and Nauss,[13] who found that the colon, damaged by chemical agents was much more susceptible to the invasion of *Entamoeba Histolytica.* It is possible that in humans the mucolytic action of lysozyme allows amebae as well as other noxious agents freer access to the cells lining the wall of the bowel.

That lysozyme is not the result of ulceration in the bowel is established by finding it in high concentration in the stools of patients who have no ulcerations in their intestine, as well as by finding variations in lysozyme concentration in the secretions removed from the surface of the intact mucosa. Likewise, low values were found in the stools of patients with ulcerating neoplastic disease of the large intestine. Moreover, in the subjects with ulcerative colitis described above, the rise in colonic lysozyme antedated the onset of bleeding and other symptoms.

Summary and Conclusions. The concentration of the mucolytic enzyme, lysozyme, has been measured in the stools of normal subjects and subjects with mucous and ulcerative colitis under a variety of circumstances and associated with widely varying life situations, emotions and attitudes. It was found that among normal subjects and subjects with diarrhea without ulceration, transitory elevations of lysozyme often occur in company with general reactions of humiliation with anxiety, resentment and guilt. Among subjects with ulcerative colitis, on the other hand, marked and sustained elevations of lysozyme were observed in such situations. These periods were characteristically marked by feelings of intense anger and hostility which were unexpressed and repressed with varying degrees of completeness, so that the subject displayed an exterior of relative calm and "sweetness". Such elevated values for lysozyme in the stool contrasted with relatively normal values in the same subjects during periods of satisfaction and contentment. Moreover, the high values were found immediately to precede episodes of exacerbation of symptoms with bleeding.

TABLE 1.—THE RANGE OF CONCENTRATION OF LYSOZYME IN STOOL SPECIMENS IN VARIOUS DISEASE STATES AND IN NORMAL SUBJECTS.

	Units per gm. Wet Stool
Normal Subjects	0.3– 1.7
Acute Congestive Heart Failure	1.2
Cancer of the Large Intestine	3.2
Mucus Colitis, (Mild Cases)	
A) Constipation	0.6
B) Diarrhea	0.4– 1.5
Ulcerative Colitis	
Remission	0.7– 1.6
Mild Symptoms	13. – 25.
Mod. Severe Symptoms	40. –100.
Regional Enteritis, Remission	0.4– 0.8
Acute (24 hour) Gastroenteritis	0.7

It is concluded from these data that lysozyme concentration in bowel secretions is highly relevant to the occurrence of ulceration, and that furthermore, variations in the production of lysozyme correspond to variations in the state of security of the organism as a whole. When the individual was meeting threats to his security arising out of problems of day to day adjustment with feelings of humiliation, guilt, anger and hostility, but was repressing them to present a serene and non-aggressive exterior, an excess of colonic lysozyme was likely to be elaborated.

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TREATMENT OF POLIOMYELITIS INVOLVING THE RESPIRATORY SYSTEM

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In 1946, 1283 cases of poliomyelitis were admitted to the communicable disease division of this hospital; in 1947, 392 cases. Many respirator cases required tracheotomies. Standardization of treatment in such cases seemed desirable and the following plan was used in the management of cases of acute bulbar poliomyelitis requiring tracheotomy while in the respirator. The discussion merely presents practical considerations in the care of these patients.

Indications for Tracheotomy. The first question raised in treatment is: will tracheotomy benefit the patient? The next question is: when should it be performed? In the absence of an oximeter to determine when the patient actually is hypoxic, the following criteria for tracheotomy were established: 1. Definite bulbar signs, usually a nasal voice and signs of interference with swallowing, the mucus pooling in the throat and posterior pharynx, endangering a free air-way. 2. Bulbar or spinal types which at first appear to be doing well, but which gradually show increasing anoxia, either in or out of a respirator. Cyanosis *per se* is often not demonstrable. Useful criteria of hypoxia are increasing pulse rate, headache and restlessness despite what appears to be an adequate respiratory exchange. 3. Atelectasis. 4. Paralysis of the vocal cords.

The advantages of tracheotomy are: the easy removal of mucus from the respiratory tract; an adequate oxygen tension is more easily maintained; emergency life-saving bronchoscopy can be performed through the wound even with the patient in a respirator; pulmonary edema may be treated more easily with positive pressure; it is unnecessary to force the patient's mouth open, sparing the patient an upsetting procedure.

Early performance of tracheotomy is stressed. If the operation is performed before any emergency sets in, the patient may be bronchoscoped, mucus removed, oxygen supplied through the bronchoscopy tube, and a more leisurely tracheotomy performed over the tube.

It often becomes necessary to do a tracheotomy on a patient who may only breathe within a respirator; in such cases, the so-called "stab" tracheotomy may be life-saving, but it should not be allowed to become necessary. Positive pressure, just as used in anesthetic procedures, may be used to carry the patient on forced breathing, during which he may be removed from the respirator and the tracheotomy carefully performed. It is desirable to have as high a tracheotomy as possible. Subsequent treatment is simplified in that the tracheotomy tube will be well out of the respirator when the collar is

in place. Pneumothorax and subcutaneous emphysema should be avoided. With trained assistants present the patient may be replaced in the respirator in about 1 minute after the tracheotomy tube is in place.

MANAGEMENT OF PATIENT IN RESPIRATOR. Once the tracheotomized patient is in the respirator continuous care by nurses trained in the management of respirator patients is of the utmost importance and the following treatment is carried out with variations to meet individual requirements. All necessary equipment essential for handling any emergency that arises must be in the immediate environment of the patient. This includes a reserve oxygen tank, a dependable suction machine with a cord long enough to prevent tension from being placed on the electrical outlet connections, rubber catheters with a few small openings around their tips and one particular catheter with an open end for removing mucus plugs. Catheters should be small enough to pass through tracheotomy tubes without applying undue force. Catheters carrying oxygen to the larynx should have numerous openings: they become plugged very quickly. The oxygen line should be supported so that it will not kink. A Wangensteen suction apparatus should be present: when needed, it is always because of emergency. Bronchoscopic equipment should be near by and a bronchoscopist available.

During the acute phase, the respirator is tipped with the head down. The angle should be steep enough to insure drainage of the bronchial tree. Shoulders should be well padded. Mucus is removed by gentle suction through the tracheotomy tube to maintain an unobstructed air-way. Normal saline containing 200 units of penicillin per ml. is instilled, prior to suctioning, a few drops at a time into the tracheotomy tube.

If the patient becomes cyanotic despite adequate suctioning, perform bronchoscopy. Some patients may require bronchoscopy 3 or 4 times in 24 hours. Penicillin is given routinely, generally 30,000 units intramuscularly every 3 hours. Oxygen passed through cool water is allowed to flow into the tracheotomy tube at the rate of 2 or 3 liters per minute. Oxygen-helium may be used for short periods. A Levine tube is passed early to facilitate administration of fluids and provide means of emptying the stomach if gastric dilatation occurs, as frequently happens. Prompt treatment can be a life-saving measure.

A properly fitted collar is very important. The back of the patient's neck should be protected by using very soft material. To keep the tracheotomy tube within easy reach of the nurse, use a metal shield which forces the sponge rubber collar forward into the respirator, and pack the resulting space around the patient's neck with toweling.

Nothing is offered orally while the patient is acutely ill. Careful attention is paid to the fluid intake. The type of fluid given is guided by blood chemical determinations. Serum chloride is checked frequently among other things: low values have been noted and are due to constant loss from many causes. Whole blood is given when needed. As a rule fluids are given intravenously for the first 4 or 5 days; occasionally the subcutaneous route is used. Intravenous amino acid preparations may be used to supply protein. Vitamins are given in customary dosage.

When sedation is required, chloral hydrate is usually given by rectum. Potassium iodide is used routinely to keep secretions less tenacious.

The speed of the respirator must be watched constantly and not be allowed to exceed 18 times a minute. *Respirators tend to run much too fast.* The pressure measured in centimeters of

water is kept between negative 16 to 18 and positive 3 to 5: children are carried at 12 to 15 negative and about 3 positive.

If the patient is unable to synchronize his breathing with the respirator, curare is used to paralyze those respiratory muscles which are receiving occasional aberrant motor impulses from the respiratory center, so that the patient will breathe only with the respirator. Synchronization of the patient and respirator is vital in the treatment of respirator patients. A dose of 1 to 2 cc. of intocostrin by the intramuscular route is preferred. One or 2 doses usually suffice, but more may be needed.

Generally when an acutely ill patient is placed in a respirator, hot packs to the chest or extremities are discontinued if the patient's fever is high. All physiotherapy is withheld the first few days. The patient should rest as much as possible. At times the nurse must keep the respirator continuously closed, using the arm ports to care for the patient's bodily needs.

Every encouragement possible is given the patient. Immediate members of the family are constantly warned against doing or saying anything which might conceivably upset the patient. Morale is an important factor in recovery.

A sincere attempt is made to segregate the new acutely ill patient from other cases which have the first few days of their illness behind them. One must guard against any possible secondary respiratory infection. Personnel as well as patients are constantly checked.

As the patient's condition improves hot packs and physiotherapy are started. Roentgenograms of the chest are taken when indicated. White blood counts and hemoglobin determinations are done at least 3 times a week. Frequent urine examinations are made. Urinary tract infections are usually treated with sulfadiazine and sulfamerazine in equal parts, when a retention catheter is considered necessary, it should be employed promptly. Enemas, and occasionally prostigmine are used to overcome distention. Blood pressure and pulse are watched constantly.

As improvement continues, a high-caloric, high-protein diet is started. As a rule it is fed through a Levine tube. Amounts are increased gradually depending on the patient's tolerance. In 8 to 10 days the patient usually receives nearly all fluids orally. Acute cases showing rather severe paralysis of the chest and extremities at onset, frequently improve remarkably within a few days. This may be due to subsidence of edema in the spinal cord. One should make every effort to get such patients out of the respirator at the earliest possible moment. Other patients are placed on a definite removal schedule according to the improvement of their condition: it may be only a minute or two out of every hour but one should attempt to lengthen the time a little each day. It is of the utmost importance for the physician to gain the patient's confidence.

Everyone working with the patient should be fully aware of all problems connected with his case. Experience has shown that when an emergency occurs in any certain patient, this same emergency may be repeated many times. Everyone should know how to handle the problem. All personnel should be cautioned to form the habit of constantly checking the pressure gauge on the respirator; it takes only a fraction of a second and may be life-saving.

As the patient improves, oxygen administration is decreased gradually and finally discontinued. Following this, if the patient's condition remains satisfactory over a period of 24 to 48 hours, the tracheotomy tube may be closed off

but not removed. One week after the patient has tolerated a closed tube it may be removed. On 3 occasions a second tracheotomy had to be performed. All were due to upper respiratory infection after the first tracheotomy had healed. These patients could not cough up secretions, the mucus became inspissated, plugs formed, atelectasis followed, and the whole procedure had to be repeated.

Above all, patience and tolerance on the part of doctors and nurses are essential. It is, in many instances, a long hard battle but one which is being increasingly won.

In 1946 we treated 129 cases of bulbar poliomyelitis, with 38 deaths including one resulting from polio-encephalitis. Tracheotomies were performed on 14 of the above patients, out of which number there were 7 deaths. In 1947 we performed 8 tracheotomies with 4 deaths. Of the 14 tracheotomies in 1946, all but one were respirator cases.

Except for individual variations the above is the treatment now used. It will undoubtedly be improved with additional experience, but during 1946 and 1947 it saved about 50% of patients of a type that previously died.

Summary and Conclusion. 1. The management of patients suffering from poliomyelitis with respiratory involvement requiring the use of a respirator has been presented.

2. The indications for, and the type of tracheotomy preferred, have been described. The value of performing an early tracheotomy has been stressed.

3. Prevention of mechanical difficulties which arise from time to time in the management of patients suffering from acute poliomyelitis and in a respirator, cannot be over-emphasized. Adequate nursing care is essential.

4. In our opinion, the treatment described here definitely has reduced mortality at least 50% in cases of acute bulbar poliomyelitis in the respirator and having had a tracheotomy performed.

By October 20, more than 2300 cases have occurred in the present epidemic. Of 248 bulbar cases over 60% have had tracheotomies performed. Early tracheotomy cannot, in our opinion, be over-stressed in the management of acute bulbar poliomyelitis. Actual statistics must await the end of the current epidemic.

THE EFFECT OF THERAPEUTIC DOSES OF ASPIRIN ON THE ACID-BASE BALANCE OF THE BLOOD IN NORMAL ADULTS*

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Recent studies on the effect of salicylate administration on the acid-base equilibrium of the blood have presented conflicting results. Fashena and Walker[6] concluded that a metabolic acidosis occurred in children receiving salicylates. In contrast, Rapoport and Guest[7,11] reported a respiratory alkalosis in children and animals. Reviews of previous work may be found in these papers.

As Erganian and co-workers[5] pointed out, the differences in results and interpretations may be due to differences in experimental subjects: "An attempt is made to compare results on anorexic younger children and infants with experimental results obtained on older children, adults, and even animals, whose usual caloric and liquid intakes have not been affected prior to or during the period of study." Also, differences in doses, time and duration of administration of the drug, and chemical determinations that were inadequate to permit complete characterization of the acid-base balance contributed to the conflicting results. Furthermore, no quantitative estimates of respiratory changes have been reported; nor have the possible side-effects of nausea, vomiting, anorexia, starvation or renal compensatory factors on the acid-base equilibrium been considered.

Because of the discrepancies mentioned, and because no studies on adults are available, it was decided to study the time relations of the effects of therapeutic doses of aspirin on the acid-base balance of the blood in normal adults and the possible pathways of displacement and recovery.

Experimental Procedure. Subjects. The subjects were 10 healthy adult males, the majority of whom were in their 20's and 30's, with an average age of 26.3 years. The youngest subject was 14 years old and weighed 149 lbs. None of the subjects had any history of allergy or aspirin sensitivity.

Experimental Methods. Resting values of all measurements for each subject were determined before medication was begun. Each subject was then given 1.3 gm. of aspirin by mouth every hour for 8 doses and 1.6 gm. at the 9th hour, making a total of 12 gm. This is one of the higher dosages recommended in the treatment of rheumatic fever.[2]

Determinations of the serum salicylate level, V_c, serum pH, total CO_2 content of the blood, respiratory volume in liters per minute and respiratory rate per minute were done every 2 hours for 16 hours† and again at the 28th hour. The temperature and blood pressure

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† In preliminary experiments, blood samples were drawn at 1-hour intervals. Since the changes were within the limits of the experimental error of the method, the 2-hour schedule was adopted.

were determined at the same time intervals.

The subjects remained in bed during the course of the experiment, except for bathroom privileges. Water was allowed freely. During the experiment subjects were given a low-fat diet in order to facilitate the colorimetric determination of serum salicylate levels.

Estimates of the acid-base equilibrium were made on samples of finger blood. The micro technique of Shock and Hastings[13] was followed for the determination of per cent red cells (V_c), the pH of the serum at 38°C (pH_S), and the total CO_2 content of the blood $[CO_2]_b$. The CO_2 tension of the blood (pCO_2) in millimeters Hg and the bicarbonate concentration of the serum $[BHCO_3]_S$ in millimols per liter were calculated from the above determinations by use of the Hastings-Shock nomogram.[8] The serum salicylate levels were estimated by the method of Keller.[9] Six-minute samples of expired air were collected in a Tissot spirometer for the estimation of respiratory volume; all air volumes were corrected to 0°C and 760 mm. pressure. Three 1-minute counts of respiratory rate were made during each 6-minute air-collection period. These counts were averaged to represent the respiratory rate per minute for that particular time.

Treatment of Data. Results are presented in terms of mean values for the group of 10 subjects. Displacements of respiratory volume, pH_S, $[BHCO_3]_S$ and pCO_2 were calculated for each subject by subtracting the control values for the individual subject from the experimental values. Mean values of the various displacements were then computed and curves plotted.

Results. Control Values. All values are well within previously established normal limits.[14] The individual and mean control values for respiratory volume in liters per minute, pH_S, $[BHCO_3]_S$ and pCO_2 are shown in Table 1.

Table 1.—Control Determinations.

Subject No.	pHs at 38°C	Vc per cent	$[CO_2]_b$ mM/L	pCO_2 mm. Hg.	$[BHCO_3]_S$ mM/L	Resp. Vol. L/Min. Std. Cond.
1	7.38	44	22.9	46.2	26.8	6.67
2	7.36	47	21.3	45.3	25.0	5.35
3	7.41	49	21.7	42.3	26.2	7.48
4	7.34	39	21.5	44.0	24.5	7.3
5	7.42	42	20.4	40.5	25.2	6.6
6	7.38	42	23.2	45.6	26.2	6.2
7	7.35	43	23.5	49.8	26.9	8.8
8	7.39	47	21.9	43.8	24.2	7.4
9	7.37	38	22.2	43.6	25.0	7.0
10	7.36	47	20.1	43.0	23.5	7.9
Mean	7.39	43.8	21.9	44.4	25.4	7.1

Clinical Symptomatology. All but 2 of the subjects developed symptoms of salicylism: tinnitus, nausea, drowsiness, headache, and anorexia. One subject vomited once, an hour and one-half after the last dose of aspirin; another vomited twice, immediately after the last dose of aspirin and again 6 hours later. Most of the symptoms developed after all the aspirin had been given and persisted for about 8 hours. One subject, however, who attained a peak blood salicylate level of 40.2 mg. per 100 cc., continued to complain of tinnitus for 48 hours after the last dose of aspirin. No systematic changes were found in body temperature or in blood pressure levels.

Serum Salicylate Levels. The administration of 12 gm. of aspirin according to the dosage schedule described above resulted in a rise in the serum salicylate level (Fig. 1). An average peak level of 39 mg. per 100 cc. (range 30.1 to 50.3 mg.) was attained 2 hours after the last dose of aspirin. After the peak was reached, the level dropped at a uniform rate for the next 18 hours at which time the average serum level was 30% of the peak concentration.

Respiratory Changes. The respiratory volume in liters per minute rose to an average maximum increment of 4.0 L./min. 2 to 4 hours after the

peak in the blood salicylate level. The average recovery 14 hours later was only one-half the total displacement (Fig. 1).

No consistent significant changes were found in the respiratory rate per minute.

Acid-Base Changes. The changes in the acid-base equilibrium of the blood were an increase in pH_s which amounted on the average to 0.06, a decrease in pCO_2 of 11 mm. Hg. and a decrease in $[BHCO_3]_s$ of 2.8 mM/L. (Fig. 1). The height of displacement in those values occurred 4 hours after the last dose of aspirin. Nineteen hours after the last dose of aspirin the acid-base changes were still displaced from the normal values.

The values of pCO_2, $[BHCO_3]_s$ and pH_s for each subject were plotted on triaxial coordinates.[15] This method of plotting acid-base changes of the blood makes use of 3 axes; one for pH_s, one for serum bicarbonate, and the other for CO_2 tension. The units on

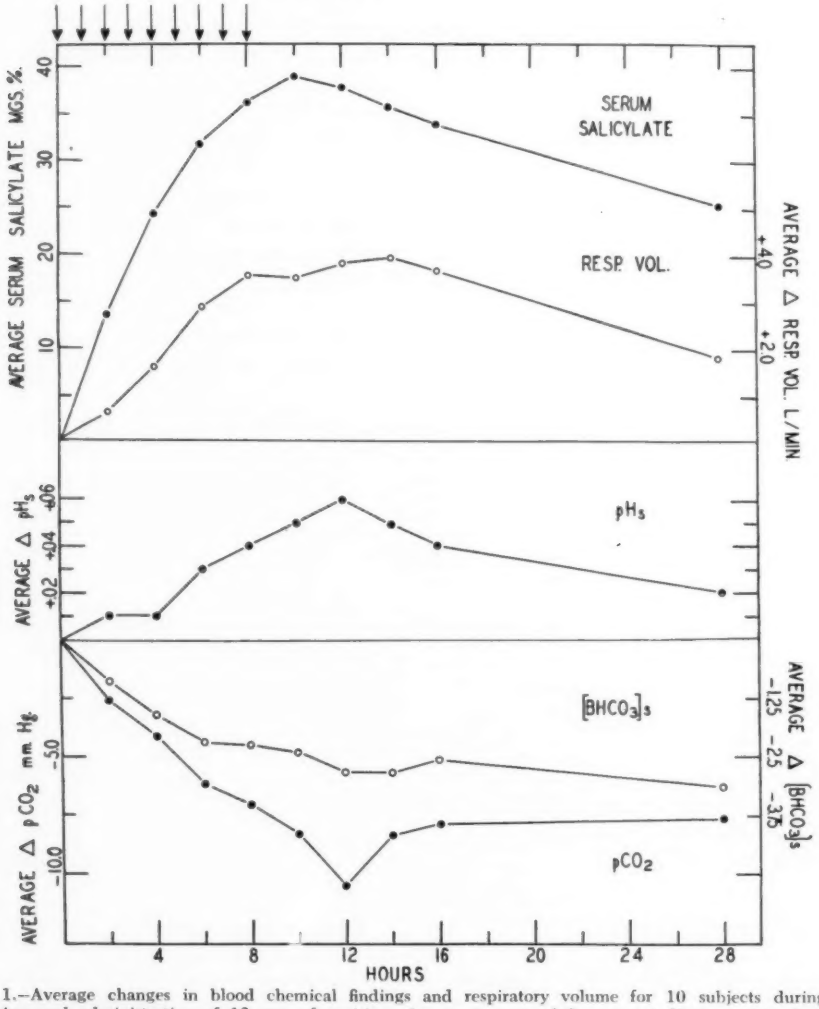

Fig. 1.—Average changes in blood chemical findings and respiratory volume for 10 subjects during and following oral administration of 12 gm. of aspirin. Arrows in upper-left corner indicate aspirin dosage at hourly intervals of 1.3 gm. each, except for the last arrow which represents a dose of 1.6 gm.

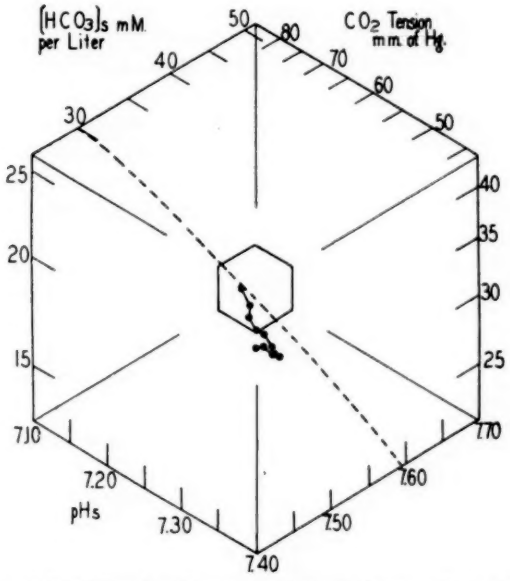

FIG. 2.—Average pathway of displacement and recovery of the acid-base balance of the blood during and following oral administration of aspirin. Each point represents determinations at 2-hour intervals; the last point is the determination at the 28th hour.

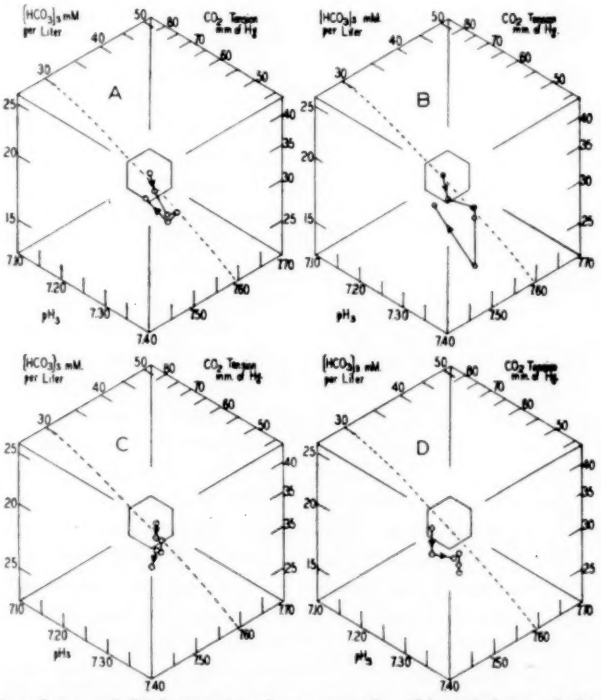

FIG. 3.—Individual pathways of displacement and recovery of acid-base balance of the blood. Each point represents values at 4-hour intervals; the last point shows values at the 28th hour.

these scales are arranged in accordance with the Henderson-Hasselbalch equation so that when any 2 variables are known, the third is determined in the coordinate system. The broken line in Fig. 2 represents the CO_2 absorption curve of whole blood when titrated with carbonic acid *in vitro*. A comparable titration with CO_2 occurs in the body by loss of or accumulation of CO_2 by the lungs. Changes in the acid-base equilibrium of the blood along or parallel to the CO_2 absorption curve are due to respiratory effects, either CO_2 excess or CO_2 deficit. It has been shown experimentally[15] that addition (or loss) of fixed acid (or base) produces changes in the acid-base equilibrium along an axis at right angles to the CO_2 absorption curve.

Average values for all subjects were calculated for each 2-hour interval for the first 16 hours and again at the 28th hour. A plot of these points shows that the pathway of displacement was along a CO_2 absorption curve for whole blood (Fig. 2).

The individual pathways of 4 of the subjects at 4-hour intervals are shown in Fig. 3. Of these, "A" (Subject 7) and "B" (Subject 8) followed the average pathway of all the subjects; "C" (Subject 3) showed a constant pH_s throughout the course of the experiment; while "D" (Subject 4) followed a pathway of a CO_2 absorption curve with no signs of recovery during the course of the experiment.

Discussion. Respiratory Changes. It has long been known that hyperpnea often occurs with salicylism. Guest and co-workers,[7] however, reported no constant hyperpnea in their subjects. This was apparently a clinical observation, since no data for either respiratory volume or rate were given. Their conclusion that salicylates produced primary hyperpnea was based on the observations of lowered CO_2 tension of the blood. In animals, Rapoport and Guest[11] found the intravenous or intramuscular administration of methyl and sodium salicylates caused a primary hyperventilation; similar results were reported by Boyle and coworkers.[3] In the present experiments, it was found that although an increase in respiratory volume (hyperpnea) occurred in all the subjects, there was no systematic increase in respiratory rate (tachypnea).

Acid-Base Changes. The literature contains numerous and conflicting reports concerning the changes induced by salicylates on the acid-base balance of the blood. The main part of disagreement has been whether salicylates produce a metabolic acidosis or a respiratory alkalosis. The confusion has arisen partly because only CO_2 content has been determined. Since this single variable is low in both conditions, it is necessary to estimate both the pH of the blood as well as the CO_2 content to determine whether an alkalosis or an acidosis exists. A discussion of the limitations of CO_2 combining-powers as a criterion of acid-base status is beyond the scope of this paper.

Following the intravenous and intramuscular administration of salicylates in animals[3,11] and the oral administration in children,[7] it was found that a respiratory alkalosis occurred. Ryder and associates[12] report the case of a 16-year-old patient with acute rheumatic fever who developed a respiratory alkalosis after a total of 26 gm. of sodium salicylate had been given by mouth in a 6-day period. It is of interest that Coburn[4] reported no untoward effects from the intravenous administration of 10 to 20 gm. of sodium salicylate in 6 to 8 hours in the treatment of acute rheumatic fever among Navy personnel.

It has been shown that the pathway of decompensation and recovery of

the acid-base equilibrium from overbreathing in normal adults follows the CO_2 absorption curve of whole blood.[15] The average pathway of displacement of the acid-base equilibrium in the present experiment also follows the CO_2 absorption curve for whole blood (Fig. 2). The recovery pathway, however, suggests a degree of renal compensation for the primary respiratory alkalosis. Previous experiments have shown that with short periods of marked hyperventilation (5 to 20 minutes) renal compensation does not occur.[15] The differences in results might be attributed to the duration (24 to 28 hours) of the hyperventilation in the experiment reported here.

GENERAL. From the preceding it is apparent that therapeutic doses of aspirin in normal human adults can produce a respiratory alkalosis that persists for at least 20 hours after the last dose of aspirin. It is known that hyperthermia *per se* may lead to hyperventilation.[10] Inasmuch as aspirin is commonly used in a variety of conditions, especially those in which fever is present, the total effect of hyperventilation from fever and from aspirin might lead to a severe respiratory alkalosis. It has been a common clinical practice in the past to give alkali to patients with salicylism. Most of the reports deal with children in whom a secondary metabolic acidosis, superimposed on an undoubtedly primary respiratory alkalosis, was present at time of admission to the hospital. These patients responded well to intravenous fluids, glucose, and alkali.[1,5] It has also been shown that the administration of sodium bicarbonate to patients receiving salicylates is followed by a more rapid reduction in the blood salicylate level than occurs otherwise.[16,17] However, the injudicious use of alkalis in patients in whom the pathway of acid-base imbalance is unknown might cause further derangement of the acid-base equilibrium in case a respiratory alkalosis were present. To prevent this, blood studies should include both CO_2 content and pH in order to determine the proper therapy.

Summary. Ten normal adults were given hourly doses of 1.3 gm. of aspirin orally for a total of 12 gm. Determinations of respiratory volume, respiratory rate, blood pressure, pulse rate, temperature, $[BHCO_3]_s$, pH_s and pCO_2 were made at 2-hour intervals for 16 hours and again at the 28th hour. Determinations of serum salicylate levels were made on the same schedule.

The administration of aspirin resulted in a respiratory alkalosis in all subjects; the respiratory volume increased (to an average maximum of 4.0 L./min), the CO_2 tension of the blood diminished (to an average maximum of 10.5 mm. Hg), the pH_s increased (to an average maximum of 0.06) and the $[BHCO_3]_s$ decreased (to an average maximum of 3.0 mM/L.).

The maximum displacement of the acid-base equilibrium occured 2 to 4 hours after the maximum blood salicylate level (average 39 mg. per 100 cc.) was reached. Twenty hours after the last dose of aspirin there was still a significant displacement of all the factors measured.

Symptoms of salicylism occurred in 8 of the 10 subjects.

No significant changes were observed in respiratory rate, pulse rate, temperature or blood pressure.

Conclusion. In normal adults the administration of therapeutic doses of aspirin may result in a primary respiratory alkalosis caused by a hyperpnea without an accompanying tachypnea.

The necessity for adequate blood studies in treating a patient with salicylism is discussed.

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STUDY OF FIXED TISSUE SECTIONS OF STERNAL BONE MARROW OBTAINED BY NEEDLE ASPIRATION

III. METASTATIC CARCINOMA IN STERNAL BONE MARROW

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The diagnosis of metastatic carcinoma can occasionally be made by finding tumor cells in films of the sternal bone marrow obtained by needle aspiration. Rohr and Hegglin[1] found metastatic tumor cells in the sternal marrow in 10 of 74 cases and Stoger[2] in 8 of 110 cases of carcinomatosis. However, many bizarre, atypical, and distorted cells are frequently seen in films of the sternal marrow and these may occasionally be mistaken for tumor cells. The diagnosis of metastatic carcinoma on this basis may therefore be open to question. A more accurate diagnosis can be made by finding nests of cancer cells in histologic sections made from sternal marrow particles by techniques previously described.[3,4] This report describes a study of histologic sections of sternal marrow obtained by aspiration biopsy from patients with malignant tumors.

Material and Methods. Aspiration biopsy of the sternal marrow was performed on 49 patients with known malignant tumors and on one patient in whom the diagnosis of carcinoma was suspected but not proven prior to sternal aspiration. Of the 49 patients with known malignancy, 29 had clinical evidence of widespread metastases and 20 had no known metastases except for involvement of regional lymph nodes. The group included patients with carcinoma of the breast, lung, kidney, prostate, gastrointestinal tract, nasopharynx, cervix, testicle, bone, and skin (Table 1). There were 5 patients in whom the primary site was unknown.

Sternal puncture was performed by the usual technique, the needle being inserted between the 2d and 3d ribs, and the material obtained was prepared by methods previously described.[4] Films were made from the first drop of marrow obtained and 1 cc. of marrow content was then aspirated. The small marrow particles were separated from the blood and suspended in plasma. The particles were then allowed to collect by sedimentation or flotation for 30 minutes in an ice box at 4° C. and the excess plasma removed. One drop of 0.25 molar calcium chloride was then added to clot the suspension of marrow particles and plasma. The resultant clot was fixed in Zenker's acetic acid fixative and prepared and sectioned by routine histologic technique. Better sections are obtained if the particles of marrow are pushed to one side with a sharp, pointed probe immediately after the calcium chloride has been added, after which all the plasma possible is aspirated with a capillary pipette. This removes an excess of plasma so that the sections contain more marrow particles relative to the amount of plasma present.

Results. Of the 50 patients, 7 were found by this technique to have metastatic carcinoma in the sternal bone marrow (Table 1). Tumor cells were found in the marrow films in 4 of these 7 patients. There were no instances in which tumor cells were observed in the film when they could not be found in histologic sections.

Metastatic carcinoma was found in the marrow of one patient in whom all clinical and laboratory findings, including extensive roentgenographic examinations, were negative (Fig. 3), and in whom sternal marrow aspiration

was performed because the history and course were suggestive of carcinoma. The marrow findings comprised the only objective evidence of carcinoma which could be demonstrated antemortem. Postmortem examination revealed an adenocarcinoma of the kidney, metastatic to the pleura, liver, and bone marrow.

Two cases of carcinoma metastatic to the sternal marrow were found in patients who were thought to have only regional metastases and were therefore subjected to operation. Both of these patients subsequently developed roentgenographic evidence of widespread bony metastases and have since died. The diagnoses were confirmed on postmortem examination.

Metastatic carcinoma was found in the sternal marrow in 2 of 10 patients with carcinoma of the breast; in 2 of 8

TABLE 1.—SUMMARY OF MATERIAL

Primary Site of Carcinoma	Number of Cases	Metastatic Lesions Found in Sternal Marrow
Breast*	10	2
Lung	8	2
Kidney	4	2
Prostrate	5	1
Gastrointestinal Tract	10	0
Nasopharynx	3	0
Uterine Cervix	2	0
Testicle	1	0
Bone (Ewing's Endothelioma)	1	0
Skin (Melanosarcoma)	1	0
Primary Site Unknown	5	0
Total	50	7

*Including one Male

TABLE 2.—DISTRIBUTION AND INCIDENCE OF METASTASES

Type of Case	Number of Cases	Metastases in Sternal Marrow
Not Known to be Metastatic*	20	2
Known to be Metastatic:		
Metastatic to Bone	12	4
Not Metastatic to Bone	17	0
Undiagnosed Prior to Sternal Biopsy	1	1
Totals	50	7

*Includes Regional Lymphnode Involvement

TABLE 3.—CORRELATION OF DEGREE OF ANEMIA WITH ACTIVITY OF MARROW

Activity of Marrow Estimated from Histologic Sections	Number	Degree of Anemia*		
		None	Moderate	Severe
Normal	35	16	17	2
Hypoplastic	9	2	6	1
Markedly Hypoplastic	6	0	2	4
Totals	50	18	25	7

*Moderate anemia: Red blood count 3.0 million to 4.0 million per c. mm. Hemoglobin between 9.0 and 12.0 gm. per 100 ml.

Severe anemia: Red blood count less then 3.0 million per c. mm. Hemoglobin less than 9.0 gm. per 100 ml.

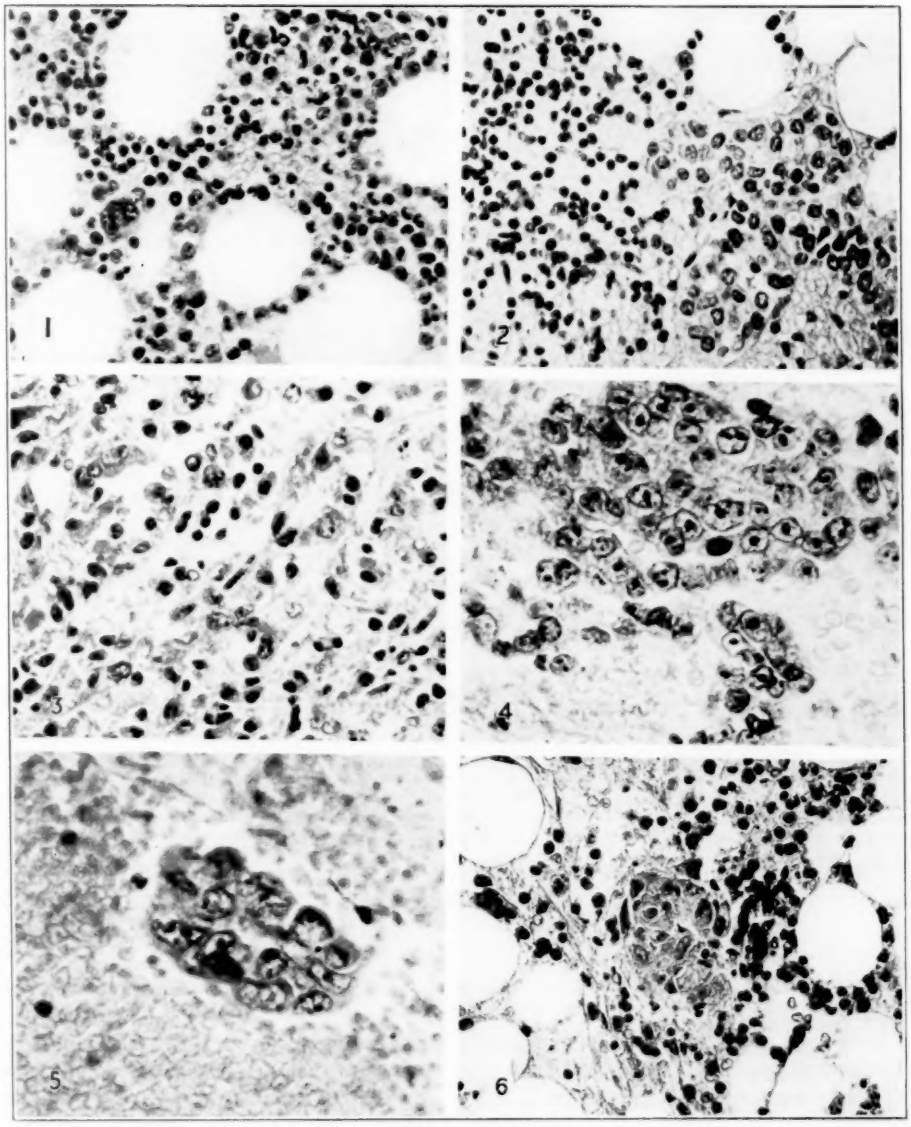

FIG. 1.—Normal marrow (450 x). FIG. 2.—Carcinoma of the breast metastatic to the sternal marrow (450 x). FIG. 3.—Carcinoma of the kidney metastatic to the sternal marrow. Note acini (550 x). FIG. 4.—Carcinoma of the prostate metastatic to sternal marrow (550 x). FIG. 5.—Carcinoma of the breast metastatic to sternal marrow (970 x). FIG. 6.—Granulomatous lesions in sternal bone marrow (550 x).

patients with carcinoma of the lung; in 2 of 4 patients with carcinoma of the kidney, and in 1 of 5 patients with carcinoma of the prostate (Table 1). Only 4 of 12 patients with roentgenographic evidence of metastases to bone were found to have metastatic carcinoma in the sternal marrow (Table 2).

Tumor cells can readily be recognized in sections of the sternal marrow. Occasionally, however, a circumscribed granulomatous lesion may be mistaken for carcinoma (Fig. 6). The tumor cells occur as a syncytium which can be clearly differentiated from loosely arranged cells of the normal

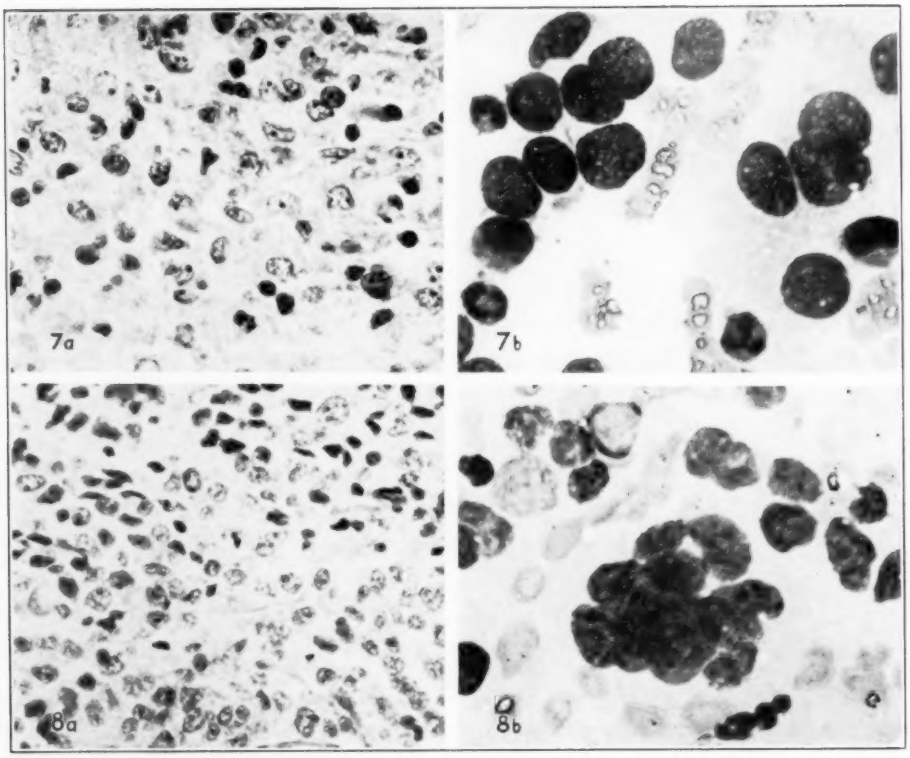

FIG. 7 A.—Renal carcinoma metastatic to sternal marrow (550 x). FIG. 7 B.—Metastatic tumor cells in marrow film. Same patient as FIG. 7 A. Wright stain (970 x). FIG. 8 A.—Carcinoma of the bronchus metastatic to sternal marrow (550 x). FIG. 8 B.—Tumor cells in marrow film. Same patient as in FIG. 8 A. Wright stain (970 x).

TABLE 4.—ANEMIA IN PATIENTS WITH CLINICAL EVIDENCE OF METASTASES

		Activity of Marrow		
Degree of Anemia	Number	Normal	Hypoplastic	Markedly Hypoplastic
None	10	8	2	0
Moderate	14	10	3	1
Severe	5	2	1	2
Totals	29	20	6	3

TABLE 5.—ANEMIA IN PATIENTS WITH METASTASES TO THE BONE

		Degree of Anemia			Histologic Activity		
	Number	None	Moderate	Severe	Normal	Hypoplastic	Hypoplastic
X-Ray Evidence of Metastases to Bone	8	3	5	0	6	2	0
Metastases Found in Histologic Section	7	1	1	5	1	2	4

marrow. They may replace the marrow entirely (Figs. 7A and 8A) or may appear as isolated nodules surrounded by relatively normal or hypoplastic marrow (Fig. 2). The tumor cells are usually large, with vesiculated nuclei and scanty cytoplasm. They tend to be basophilic when stained with hematoxylin and eosin, and mitotic figures are common. In most cases there is a marked tendency toward anaplasia. The diagnosis of metastatic carcinoma was not made on the basis of scattered abnormal cells, although occasionally isolated cells of abnormal appearance were present and were highly suggestive of carcinoma.

Tumor cells in the bone marrow films appeared as large, bizarre cells, usually in groups or clumps, with ill-defined, faint blue cytoplasm, when stained with Wright's stain (Figs. 7B and 8B). The cytoplasm was frequently entirely absent. The nucleus usually appeared to be densely hyperchromatic and reticulated. One to 3 "robin-egg blue" nucleoli were usually visible. Basket cells were common. Occasionally the cells appeared to be in the process of division. When such cells are present in large numbers, a diagnosis made from the Wright stained film is probably reliable. The occurrence of large numbers of such cells is uncommon, however.

Differential counts of the cells in the bone marrow films revealed no characteristic pattern. Occasionally the granulocytic/erythroid rate was high, especially in hypoplastic marrows. Plasma cells were found in a higher percentage than usual in a few patients with advanced carcinomatosis, but this is not a consistent or characteristic finding.

A marked increase in plasma cells was noticeable in the histologic sections in 5 cases (3 carcinomas of the lung, 1 of the breast, and 1 of the kidney). Metastases were likely in these patients, from a clinical standpoint, but they were not found in the sections. Hemosiderin deposits were noticeably increased in 2 of these cases. These 2 patients were severely anemic. The occurrence of hemosiderin deposits suggests an inability to utilize iron in hematopoiesis, as occurs in certain anemias associated with infection. Solitary lymph follicles were present in 6 cases.

The occurrence of anemia and its correlation with the activity of the bone marrow as estimated from histologic sections was investigated. In the entire group of 50 patients, 18 had no anemia, 25 had moderate anemia (red blood count 3 to 4 million per cu. mm., hemoglobin 9 to 12 gm.), and 7 had severe anemia (red blood count less than 3 million per cu. mm., hemoglobin less than 9 gm.). A normally active bone marrow was present in 35 patients, a hypoplastic marrow in 9 patients, and a markedly hypoplastic marrow in 6 patients (Table 3).

Of the 29 patients in whom metastases were evident clinically, 10 had no anemia, 14 had a moderate anemia, and 5 had a severe anemia. Twenty of these patients had a normally active bone marrow, 6 a hypoplastic marrow, and 3 a markedly hypoplastic marrow (Table 4).

Five of the 7 patients in whom metastases were found in the bone marrow had a severe anemia, 1 had a moderate anemia, and 1 had no anemia. In 4 of the 5 patients with severe anemia, the bone marrow samples studied showed almost complete replacement of normal elements with tumor, and 1 had a hypoplastic marrow. The patient without anemia had a hypoplastic marrow and the patient with moderate anemia had a normal marrow (Table 5).

In 8 patients with roentgenographic evidence of bony metastases, but in whom tumor cells were not found in the marrow sections, 5 had a moderate

anemia and 3 had no anemia. Six of these patients had a normal marrow and 2 a hypoplastic marrow (Table 5).

Discussion. The incidence of metastasis to the sternal marrow which occurred in this series is probably considerably higher than the incidence of metastasis in all patients with carcinoma. Many of the patients were deliberately selected in whom metastatic lesions were demonstrable, especially to bone. If more patients with early carcinoma or with carcinomas that do not commonly metastasize to bone had been studied, it is likely that the incidence of metastasis to marrow would have been much lower.

Metastatic lesions were found only in patients with carcinoma of the breast, lung, kidney, and prostate, all of which commonly metastasize to bone. The ability to demonstrate metastatic lesions in 2 patients who underwent operation when other evidence of metastases was lacking, and the absence of any other objective evidence of cancer in another patient, suggests usefulness of the method. It was occasionally impossible to obtain marrow from patients with known metastatic lesions to the bone. This was especially true of patients with carcinoma of the prostate and was attributed to sclerotic or fibrotic changes in the marrow, which prevented aspiration through the needle.

It is obvious, of course, that a negative finding does not preclude the possibility of a metastatic lesion in the marrow. In view of the lack of uniformity of the bone marrow the entire tissue block should be sectioned serially and representative portions studied for metastatic lesions.

Interpretation of the anemia in these patients is difficult. The degree and type of anemia in patients with carcinoma may be affected by loss of blood and inadequate food intake, in addition to which other unknown factors may contribute to failure of proper hematopoiesis. Anemia was present in most, but not all, cases when metastatic tumor was found in the histologic sections. Normal blood values and a normally active marrow occurred not infrefrequently in patients with roentgenographic evidence of bony metastases and the same was true of patients with metastases in sites other than bone. Inspection of the data reveals that in many instances there was no correlation between the degree of anemia present and the activity of the marrow, as demonstrated by study of the aspirated particles.

Summary and Conclusions. Of 50 patients with malignant tumors, 7 were found to have metastatic lesions in the sternal bone marrow as demonstrated in tissue sections of particles obtained by needle biopsy. This does not represent a true incidence, however, the over-all percentage for all types of carcinoma probably being much lower. Sternal marrow metastases were found only in the case of those tumors which have a tendency to metastasize to bone. Metastatic lesions were found in the marrow in 2 patients after operations for carcinoma of the breast and lung, respectively. In 1 patient a metastatic lesion in the marrow was the only positive antemortem evidence of carcinoma. This would indicate that the procedure might be of benefit preoperatively in cases of carcinoma which are likely to metastasize to bone, and as a diagnostic tool in selected cases. Anemia was not a consistent finding and no correlation could be drawn between the occurrence of anemia and the activity of the bone marrow.

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THE BLOOD PICTURE IN LEPROSY

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A few papers on the blood picture of leprosy have already been published. No general or definite agreement, however, has ever been reached, and different workers give conflicting results.

It must be emphasized that we do not by any means regard the blood picture as being of such paramount importance that, for instance, it would necessarily aid in the diagnosis or prognosis of the disease. At any rate, the problem is still unsolved. Certain changes, however, do occur, and the interpretation of such changes should interest the leprologist and the hematologist alike. What is more, we feel that since all our patients are Chinese our results may be regarded as an independent contribution for comparison with those obtained from patients of other nations.

It is not proposed to review the literature exhaustively. Some of the more important papers must be mentioned. The most complete is apparently that of Cerri (1942),[2] who studied in Italy the blood and bone-marrow of 35 lepers. A list of 47 references was given. Of the blood, estimations were made of the hemoglobin, the number of red and white cells and the differential white cell counts. Leukopenia of 2,600 and 4,150 respectively was found in 2 cases, leukocytosis up to 14,850 was found in 5, anemia was a constant feature, nearly always hypochromic, with some degree of anisocytosis, and rarely poikilocytosis; neutral metamyelocytes were also present but not in large numbers, non-segmented neutrophils were more common, up to 35% of the neutrophils.

Arisumi (1931)[1] working in Formosa, found that the red corpuscles were reduced in number and a fairly high proportion of basophil-punctate and polychromatophil cells were seen, together with anisocytosis and poikilocytosis, but no nucleated form. The leukocytes were always increased in number, especially in advanced nodular cases, with some decrease in lymphocytes. The eosinophils were few, but might become increased. The hemoglobin was decreased in proportion to the activity of the disease, and the hemoglobin index was low.

In 31 cases in Sardinia, Pinetti (1931)[8] found a slight anemia, a very variable Arneth count, often shifted to the right, and seldom observed eosinophilia.

Some attempts have been made to associate the blood findings with the progress and prognosis of the disease. Thus, Peschkowsky (1934)[7] observed that monocytosis was an unfavourable sign as it was associated with the formation of fresh granulomata with proliferative chronic inflammation. On the other hand, lymphocytosis was favourable in most cases, as it coincided with a period of convalescence and decrease of the inflammatory process. Polymorphonuclear leukocytosis accompanied exacerbations of the disease with suppurative inflammation and subsequent destruction of the bacilli in the polymorphonuclear neutrophils. Fonte

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(1941)[4] reported that exacerbations of the disease, acute or subacute, were preceded by leukocytosis, mainly of the polymorphonuclear elements; regressions of the lesions by reduction of these and increase of large mononuclears; in convalescence, both were reduced with corresponding increase of small lymphocytes.

The reason for considering these findings will be appreciated when they are compared with our results.

Present Study. Attached to the West China University Hospital, Chengtu, is a leprosarium, superintended by Dr. W. Crawford, with a normal capacity of 45 beds. During the period between November, 1945, and June, 1947, the blood picture of 36 lepers was examined.

The work was interrupted for some time by the departure of the senior author (S.K.). Later, beginning from October, 1946, when promin treatment was initiated, it was found necessary to check periodically the blood picture of those who received treatment, and so this work was further substantiated and completed. In the earlier period, we personally did several determinations of the red blood cells, hemoglobin, white blood cells and differential white cells, of each of the 19 patients then in the leprosarium. After the first few rounds, we wanted to find out if any of the patients had other parasitic infestations. As no parasites were encountered in the blood smears, the stools of all were examined, and treatment for ascaris and hookworm, the 2 principal findings, were given where indicated. More counts were made after treatment and a second examination of the stools, which were then all negative. The second part was entirely carried out by the technicians in the Hematology Department of the Hospital, directed by Dr. Y. T. Beh. Two complete hemograms of each of the 27 patients were done. Among these 27, 10 were in our first batch of 19, so the total number of patients examined was 36.

It should be stated that these patients had received various forms of treatment for leprosy, chaulmoogra oil, moolgrol, diphtheria toxoid, alepol and promin. Whether these drugs have any effects on the blood pictures or not must therefore be considered. Generally speaking, we think that they have none, for two reasons. First, the pharmacological actions of these drugs have not been known to cause any actions in the peripheral blood elements. The case of promin is somewhat different. It is stated that the most frequent toxic manifestation of promin is a slow destruction of the erythrocytes; also, a small number of patients may develop leukopenia. Cases 1 to 27 were those who received promin. Hemograms were done for everyone of them before treatment was started, and repeated about 3 months later. From the results of the 2 hemograms little change, however, was observed in both the red and white cells counts. The relative leukopenia of Cases 15 and 20 (see Table 2) was present at the beginning and was unaffected by promin. Therefore, we think that promin, like the other drugs, did not have any noticeable effect on our results. Also, when the first part of this work was being done none of the patients had been receiving any specific treatment, which was stopped for some time because there was a universal lack of supply of drugs. A second thought would be to associate some of the changes with the 2 generally accepted types of leprosy, the neural and the lepromatous. A complete physical survey of the patients was done, and they were separated into these 2 divisions. We might also say that none of these patients had any intercurrent diseases, as each of them had been thoroughly checked before admission, and each

of them was proved to have leprosy by biopsy. While doing the hemograms, the Kahn tests of all but 2 of the 27 patients were found to be positive. It should be remembered, however, that it has been generally accepted that leprosy as well as syphilis gives a positive Kahn test. (Rogers and Muir, 1946,[9] and Strong, 1943.[10])

Results. The results of our studies are given in Tables 1 and 2. For the morphological studies of the red cells and the differential white counts, Wright's stain was used throughout, and the Wintrobe hematocrit was used for all hematocrit determinations of the red cells.

As stated above, for Cases 1 to 27, two complete hemograms were done at different periods, and for our original 19 cases, all the counts were repeated for not less than 5 times. Two-hundred white cells were counted in the differential white counts. All figures given in the tables represent the mean values.

The standard figures which we have adopted as 'normal' are those given by Wintrobe (1946).[12] Wu and Tsai

TABLE 1. RED BLOOD CELL DETERMINATIONS IN 36 CHINESE LEPERS

Case No.	R.B.C. Total Count millns. per c.mm.	Hgb. gm. per 100 cc.	Vol. Packed R.B.C. cc. per 100 cc.	Mean Corpuscular Volume (c.μ.)	Mean Corpuscular Hgb. (γγ)	Mean Corpuscular Hgb. Conc. %	Reticulocytes per cent	Sedimentation Rate mm.	Change in Sedimentation Rate	Type of Anemia
Normal Values	*5.4 ± 0.8*	*16 ± 2*	*47 ± 7*	*87 ± 5*	*29 ± 2*	*34 ± 2*	*0.5–1.5*	*0–10*		
1	4.45	12.0	44	97	26	29	0.1	19	increased	macrocytic hypochromic
2	5.01	14.2	43	86	28	32	0.1	10	increased	—
3	5.31	11.3	45	84	21	25	0.1	6	—	normocytic hypochromic
4	4.12	10.1	35	85	25	29	0.1	20	increased	normocytic hypochromic
5	4.56	9.7	37	80	21	26	0.1	12	increased	microcytic hypochromic
6	3.64	8.4	32	89	23	26	0.1	8	—	normocytic hypochromic
7	4.64	13.3	37	80	28	35	0.1	28	increased	—
8	4.65	12.7	41	89	25	31	0.4	28	increased	normocytic hypochromic
9	3.69	10.0	41	110	27	24	0.1	3	—	macrocytic hypochromic
10	4.65	11.9	42	91	26	29	0.1	32	increased	normocytic hypochromic
11	3.94	11.0	40	102	28	27	0.3	19	increased	macrocytic hypochromic
12	4.24	11.6	35	85	20	30	0.1	5	—	normocytic hypochromic
13	4.18	10.1	38	92	25	26	0.3	20	increased	normocytic hypochromic
14	4.83	10.4	41	85	23	27	0.1	32	increased	normocytic hypochromic
15	3.55	9.8	32	91	28	31	0.2	21	increased	—
16	5.34	11.6	41	77	21	28	0.1	18	increased	microcytic hypochromic
17	3.45	9.2	37	102	26	25	0.5	20	increased	macrocytic hypochromic
18	4.50	12.1	49	110	27	24	0.1	25	increased	macrocytic hypochromic
19	4.27	10.2	36	89	25	28	0.9	22	increased	normocytic hypochromic
20	4.62	13.3	44	94	28	30	0.1	12	increased	—
21	4.01	10.4	34	85	25	30	0.1	26	increased	normocytic hypochromic
22	3.42	6.6	30	88	19	22	0.1	12	increased	normocytic hypochromic
23	4.60	12.7	43	93	27	29	0.1	24	increased	normocytic hypochromic
24	5.19	12.1	49	97	23	24	0.1	23	increased	macrocytic hypochromic
25	4.02	10.3	41	102	25	24	0.1	44	increased	macrocytic hypochromic
26	3.26	8.7	24	75	27	36	0.1	23	increased	microcytic
27	3.68	10.1	30	83	27	33	0.1	23	increased	—
28	3.62	10.6								
29	4.48	11.6								
30	3.53	10.9								
31	5.05	11.9								
32	3.21	12.1	.....			Not Done		.....		
33	3.61	10.4								
34	4.28	10.1								
35	3.80	8.7								
36	3.52	8.1								
Average	4.20	10.7	38	90	24	29	0.17	19		
Standard Deviation	−1.2	−5.8	−9	+3	−5	−5	?	+9		

TABLE 2. WHITE BLOOD CELL DETERMINATIONS IN 36 CHINESE LEPERS

Case No.	Total count thou. per cu. mm.	Differential Count per cent						Summary of Results						
		stab.	poly.	eosin.	lympho.	mono.	baso.	leukocytosis	leukopenia	shift to left	shift to right	eosinophilia	lymphocytosis	monocytosis
Normal Values	5–10	3–5	54–62	1–3	25–33	3–7	0–0.75	>10,000	<5,000			>3	>33	>7
1	10.4	12	41	3	33	11	—	+		+				+
2	11.0	7	50	3	37	3	—	+		+			+	
3	8.8	8	55	3	27	7	—			+				
4	9.5	9	47	2	37	5	—			+			+	
5	7.0	8	18	4	51	18	1			+		+	+	+
6	13.6	14	21	13	42	9	1	+		+		+	+	+
7	5.9	10	22	2	54	11	1			+			+	+
8	9.4	12	35	21	22	10	—			+		+		+
9	10.0	18	36	3	35	7	1			+			+	
10	5.3	14	35	1	39	11	—			+			+	+
11	9.2	6	44	4	42	4	—			+		+	+	
12	6.5	12	29	3	50	6	—			+			+	
13	7.9	15	44	10	29	2	—			+		+		
14	12.0	13	33	—	45	9	—	+		+			+	+
15	5.0	19	20	3	49	9	—		+	+			+	+
16	12.5	10	49	8	31	2	—	+		+		+		
17	9.7	5	42	—	50	3								

16	12.5	10	49	8	31	2	—	+		+		+		
17	9.7	5	42	—	50	3	—				+		+	
18	5.9	7	48	3	37	5	—			+			+	
19	8.4	4	22	1	63	10	—				+		+	+
20	4.5	21	47	—	29	3	—		+	+				
21	6.0	10	41	1	48	—	—			+			+	
22	9.0	17	43	11	17	11	1			+		+		+
23	5.9	14	46	1	34	5	—			+			+	
24	7.0	2	57	2	28	11	—				+			+
25	10.3	19	34	13	31	3	—	+		+		+		
26	7.0	11	53	1	20	15	—			+				+
27	7.4	28	38	1	26	7	—			+				
28	8.2	—	45	4	25	25	1				+	+		+
29	8.0	2	22	1	50	25	—				+		+	+
30	9.0	—	19	10	34	36	1				+	+	+	+
31	12.6	1	62	1	26	9	1	+			+			+
32	7.4	2	50	3	33	12	—				+			+
33	12.3	3	69	13	12	3	—	+			+	+		
34	9.5	2	58	9	25	5	1				+	+		+
35	15.2	1	51	17	18	13	—	+			+	+		+
36	28.8	1	32	2	57	8	—	+			+		+	+
Average	8.8	9	40	5	36	10	0.25	10 (28%)	2 (5.5%)	24 (66.7%)	12 (33.3%)	13 (36.1%)	19 (52.2%)	19 (52.2%)

(1940)[13] had previously worked out the normal hematological standards of 310 adult Chinese, and Kuo (1937)[5] the normal variations of the leukocyte counts of a group of young Chinese. It is useful to compare their results with Wintrobe's figures (Table 3).

From Table 3 we know that the hematological standards among the Chinese do not deviate much from the general average. The only comment we might make is the relatively high

Table 3. Chinese Normal Hematological Standards Compared with Wintrobe's

	Wintrobe	*Wu and Tsai*	*Kuo*
R.B.C. (millions p. cu. mm.)	5.4 ± 0.8	5	
Vol. packed R.B.C.	47 ± 7 cc.	42 cc.	
Hemoglobin	16 ± 2 gm.	13.6 gm.	
M.C. Vol.	87 ± 5 c. μ	85.4 c. μ	
M.C. Hb.	29 ± 2 $\gamma\gamma$	27 $\gamma\gamma$	
M.C. Hb. Conc.	34 ± 2%	32%	
W.B.C. (average) per cu.mm.	7,000	6,800	7,913
Stab. (%)	3–5		14.5
Poly.	54–6.		49.0
Eosin.	1–3		2.8
Lympho.	25–33		26.5
Mono.	3–7		6.4
Baso.	0–0.7		0.3

count of the young polymorph or stab cells. It is also our experience and impression, gained by examining normal blood smears, that this count is always a little higher than normal. Explanations which can be offered aside from racial differences include: hidden foci of infection, dental conditions, skin lesions and perhaps intestinal parasitic infestations.

(*1*) *Red Blood Cells.* From Table 1 it will be readily seen that anemia is rather constant, although there was no instance of a severe nature. The lowest values were thus: R.B.C. above 3 millions, hemoglobin, 6.6 gm., M.C.V. 75 c.μ., M.C.H. 19 $\gamma\gamma$ and M.C.H.C. 22%. We found 7 instances of macrocytic anemias, 12 instances of normocytic anemias, and 3 instances of microcytic anemias, all hypochromic in character. From our study of the morphology, we observed no anisocytosis or poikilocytosis of any marked degree, and certainly no instance of basophilic-punctate or chromatophilic red cells, such as described by Arisumi (1931).[1] The reticulocyte counts were distinctly low, the highest being 0.9%, the average being less than 0.2%. The technique used was that recommended by Wintrobe, the film being made after mixing a drop of blood with a drop of cresyl blue, together. We are quite unable to account for the low figures. The sedimentation rate was raised in all except 4 cases (average 19 mm.); this is in agreement with other records, such as Manson-Bahr (1945).[6]

(*2*) *White Blood Cells.* We found that leukocytosis was by no means a constant feature, and when present, was only of a moderate degree. Thus, it was found in 10 cases, or 27.7%. Here it is our impression that the lepromatous lesions might account for the increase; the last 2 cases, 35 and 36, with the highest counts, were prominently of this lepromatous type. Among these leukocytosis cases, neutrophilia was never marked, and the increase was therefore due to the proliferation of the mononuclear elements. Only 2 cases had leukopenia, of 5,000 and 4,500 respectively; the counts were made before they had received any promin; indeed, treatment was withheld for a while because of these find-

ings before it was actually started. The shift of the neutrophil count was definitely to the left, 24 cases or 66.7%, rather than to the right, 12 cases or 33.3%. We do not agree therefore with Pinetti (1931),[8] who often found a shift to the right. Dharmendra (1939),[3] like us, in a study of 70 cases found a shift to the left. However, there is evidence already furnished that a shift to the left is usually encountered in the blood picture of the Chinese, and hence, this is not a significant finding.

The high incidence of eosinophilia is a notable feature. Out of 36 cases, there were 13 instances, or 36.1%. The range was 4-21%, and average 5%. Wanser (1936)[11] observed 11 instances out of 26 cases, with a range of 6 to 16%. It was this finding which prompted us to initiate stool examinations; subsequently to treatment, the counts were not affected or lowered, even though the stools had become negative. Wanser (1936)[11] concluded that the increase was due to complications, as in his case, the counts fell to normal after all worms were expelled. We still wish to maintain that the eosinophilia is related to the lepromatous type of lesions; Cases 8, 33, 34, and 35 were prominently lepromatous, and they had the highest eosinophil counts. Again, we do not subscribe to the findings of Pinetti (1931),[8] who seldom observed eosinophilia. We might emphasize that despite the heavy incidence of intestinal parasitism among the Chinese, the eosinophils are not normally raised, as shown by the figures of Kuo (1937).[5]

The high incidence of lymphocytosis and monocytosis speaks for itself. There were 19 cases, or 52.2% of the total, of each. The range of the lymphocytes was 34 to 63% (average 36%) and that of the monocytes 8 to 36% (average 10%). It is not surprising to find these mononuclears increased in such a chronic disease as leprosy. But the question of their association with the prognosis of the disease arises. Like Peschkowsky (1934),[7] and Fonte (1941),[4] we tried to solve this problem by additional clinical observations. During the period of all our blood examinations, which covered nearly 2 years, there was certainly no clinically marked flare-up or deterioration among any of the severer cases, and despite treatment, the lesions, neural or lepromatous, were likewise stationary. All the patients were as well as could be expected, though some complained occasionally of 'rheumatic' pains. Of progress or prognosis, favourable or unfavourable, neither lymphocytosis nor monocytosis in our cases provided us with any clues. But in the light of the observation of the other workers, we believe that these mononuclear elements would serve as useful indicators, at least, of the establishment of disease.

Summary and Conclusions. The hematological findings of 36 cases of proved leprosy in West China were as follows: anemia, mainly normocytic and hypochromic; increased sedimentation rates; infrequent leukocytosis, of moderate degree; marked shift to the left of the white cell count; with high incidence of eosinophilia, lymphocytosis and monocytosis. The significance of such findings was discussed.

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EFFECT OF HESPERIDIN METHYL CHALCONE (VITAMIN P) ON DIABETIC RETINOPATHY

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Under proper dietary management and with the aid of Insulin therapy, most diabetic patients can be kept in a reasonably normal state of nutrition and in satisfactory metabolic balance as far as gross glycosuria and freedom from frank symptoms of diabetes are concerned. Nevertheless, these clinical criteria of control of the disease have proved inadequate to protect the diabetic against the onset of vascular disease if he lives long enough. This fact has recently been emphasized by Dolger[3] who showed that in a group of 200 patients whose diabetes was observed within a period of 25 years' duration, there was evidence of vascular disease in every case. He concluded that "present day treatment of diabetes has failed to avert the accelerated vascular damage which is an associated phenomenon and not a complication". That this finding may not be invariable is indicated by 2 cases in the Indianapolis series (D.D. and K.R.), whose juvenile diabetes has extended well over 20 years, and who show no demonstrable retinal, renal, or other vascular damage whatsoever. How to prevent or retard vascular degeneration is a problem and a challenge.

The most common and in many cases the earliest manifestation of vascular involvement is the appearance of hemorrhages and exudates in the retina. There have been no satisfactory methods of treatment of these retinal lesions, and consequently a therapeutic measure which offers any hope is worthy of consideration. If the progressive course of diabetic retinopathy could be arrested, similar damage to the vascular system in other parts of the body might likewise be favorably influenced.

The early investigations by Szent-Gyorgyi[1] on vitamin C led him to believe that a substance other than ascorbic acid was responsible for the petechial hemorrhages which appear in deficiency states. He identified the substance as a mixture of the flavone glucosides of hesperidin and eriodictyol. There was evidence that the absence of this substance increased capillary permeability and so it was called vitamin P. The vitamin P used in the present study was hesperidin methyl chalcone (H.M.C.); it is derived from the rinds of citrus fruits. (Rutin, another of the flavone glucosides, also has vitamin P activity, differing from hesperidin methyl chalcone in that its potency, according to Scarborough,[3] is about one-half that of pure hesperidin.)

Vitamin P has been suggested as a means of control of the hemorrhagic manifestations of certain disorders.[5,9,10,12,14] The present study was undertaken to determine the effect of vitamin P on the retinal hemorrhages of diabetes. As a part of the investigation additional information was sought in the hope of throwing some light on other factors which might be associated

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with the appearance of retinal hemorrhages. It is well known that diabetic retinopathy tends to be progressive. There is a wide variation in the rate at which fresh hemorrhages and exudates appear, and these lesions may undergo spontaneous absorption for no apparent reason. It is difficult, therefore, to evaluate fully any therapeutic agent unless a large series of cases are followed for a long period. The number of patients so followed in our series is too small to be of statistical significance, but some information has been obtained by a careful study of individual cases.

Twenty-two diabetic patients with retinal hemorrhages have been treated with hesperidin methyl chalcone. The daily dose was small in the beginning but was gradually increased when it became apparent from studies of the effects of administration of massive doses by Kirtley and Peck[8] that there were no side reactions from the drug. All but one of the patients ultimately received between 100 and 300 mg. of the drug daily, and in some instances these doses were exceeded considerably for short intervals.

Systematic examinations of the fundus oculi were made through a dilated pupil by the same examiner (M.M.) every 2 to 3 months during the period of observation. Each case was followed for an average time of 15½ months, the shortest period being 4 months and the longest 32 months. Every patient showed one or more of the typical types of retinal hemorrhages seen in diabetes. Particular attention was given to the hemorrhagic lesions, since capillary damage may be responsible for their appearance. If the exudates seen in diabetic retinopathy represent the extravasation of plasma from vessels, they may also be a manifestation of increased capillary permeability. On the basis of ophthalmoscopic findings the retinal lesions were arbitrarily divided into 2 groups, early and moderate. Those patients with punctate hemorrhages which did not exceed 5 in number, with or without small waxy exudates, were classified as having early diabetic retinopathy. Where punctate hemorrhages were more numerous and larger deep hemorrhages were present, the retinopathy was classified as moderate. Many of the patients in the latter group showed extensive areas of retinal exudation and a few had cotton wool patches.

Blood Proteins. Schneider, Lewis, and McCullough[15,16] determined plasma protein levels in diabetics by electrophoretic methods and found that the albumin level was usually low in untreated or poorly controlled cases. Total proteins approached normal since there was an increase in the globulin. Adequate treatment and high protein diet restored the albumin to normal levels and in some instances this was accompanied by an improvement in the retinal lesions. Our studies, however, do not indicate any significant alteration in plasma proteins as determined by the modified biuret method of Kingsley.[7] A summary of the average protein levels of 23 diabetics is given in Table 1. Individual values were within normal range in 3 patients without retinopathy, 13 with early retinal lesions, and 7 with more advanced hemorrhages and exudates. Protein intake was not less than 1 gm. per kg. of body weight and did not exceed 100 gm. daily. All but 3 patients were regarded as being under satisfactory diabetic control.

Table 1.—Blood Proteins in 23 Cases.

Appearance of Retina	Number of cases	Albumin (Average)	Globulin (Average)	Total Proteins (Average)
Normal	3	4.65	2.83	7.51
Early Retinopathy	13	4.79	2.90	7.69
Moderate Retinopathy	7	4.60	3.07	7.67

PROTHROMBIN TIME. Since diabetic retinopathy is characterized by the presence of hemorrhages, prothrombin determinations were made in 33 cases, using the method of Quick. A summary of the results appears in Table 2. Three out of 4 control cases with normal fundi had normal prothrombin times. An increase in prothrombin time was found in 6 of 15 patients with early diabetic retinopathy and 11 of 12 patients with moderate retinopathy. This finding is not in agreement with that of MacLean and Brambel,[11] who reported a decreased prothrombin time in their series of cases treated with dicumarol and rutin. There was no correlation between increased capillary fragility and increased prothrombin time (Table 2). Whether there is any direct relationship between changes in prothrombin time and diabetic retinopathy awaits further study.

CAPILLARY PERMEABILITY. Capillary permeability was measured by positive pressure using a blood pressure cuff inflated to diastolic pressure and maintained at that level for 3 minutes. The number of petechiae appearing in the anticubital fossa within an area 1 inch in diameter were counted. Capillary permeability was considered to be increased if more than 20 petechiae were present. Our findings confirm the reports of others that diabetics with retinal changes show increased capillary fragility in most cases.

Results. Findings are tabulated in Table 3. Six patients (Cases 1 to 6) showed a definite increase in retinal hemorrhages while undergoing treatment with hesperidin methyl chalcone. Case 5 was an employee of the hospital who was examined at frequent intervals. She developed pre-retinal hemorrhages which would often appear after a coughing paroxysm. They produced a positive scotoma and the patient sought advice as soon as possible. Some hemorrhages absorbed while others extended into the vitreous where they became organized into bands of retinitis proliferans. In the right eye the retina was detached by the contraction of one of these bands. The appearance of hemorrhages and the course they took was not influenced by taking hesperidin methyl chalcone for a period of 32 months. (This patient also received massive doses[8] up to 15 gm. daily without apparent improvement.)

In 5 patients (Cases 7 to 11) the retinal lesions remained stationary. No fresh hemorrhages or exudates appeared, and those that were present showed no evidence of absorption. The administration of hesperidin methyl chalcone may have prevented any new lesions from developing; or such cases may represent the group of diabetic patients whose retinopathy remains unchanged for long periods.

Five patients (Cases 12 to 16) showed improvement. Hemorrhages absorbed and in Cases 13 and 15 cotton wool exudates disappeared. In Case 12 the patient was used as a control after the hemorrhages absorbed. Hesperidin methyl chalcone was discontinued and fresh hemorrhages reappeared in 7 months. Hesperidin methyl chalcone was administered again and the hemorrhages reabsorbed. Unless there was an unusual coincidence of events, it would seem that the medication played some part in the improvement of the retinal lesions. The effect which hesperidin methyl chalcone had on the retinopathy of other patients in this group cannot be definitely established since spontaneous absorption of hem-

TABLE 2.—PROTHROMBIN TIME AND CAPILLARY FRAGILITY.

Appearance of Retina	Number of Cases	Prothrombin Time		Capillary Fragility		Duration of Diabetes (Yrs.)
		Normal	Increased	Normal	Increased	
Normal	4	3	1	3	1	6¾
Early Retinopathy	15	9	6	6	9	7¼
Moderate Retinopathy	13	1	12	7	6	10

TABLE 3.—SUMMARY OF CASES.

Case No.	Name	Age and Sex	Duration of Diabetes (years)	Blood Pressure	Capillary Fragility		Control & Total Insulin	Retinopathy	Daily Dose of H.M.C. and Months of Treatment	Months H.M.C Treatment Administered	Results
1	D.G.	68 F	1	110/50	N	N	Good 15 U	Early	15 mg. - 3 mos. 75 mg. - 4 mos. 100 mg. - 1 mo. 150 mg. - 1 mo. 200 mg. - 8 mos.	17	Hemorrhages increased and cotton wool exudates appeared
2	F.J.	52 F.	1	150/90	100	0	Fair 80 U	Moderate	15 mg. - 11 mos. 100 mg. - 2 mos. 200 mg. - 8 mos.	21	More hemorrhages appeared while receiving 200 mg. daily
3	A.W.	56 F.	2	130/80	150	0	Good 22 U	Early	300 mg. - 5 mos.	5	More punctate hemorrhages appeared in right eye.
4	C.W.	54 F.	1	150/70	20	20	Good 0	Early	15 mg. - 4 mos.	17	Punctate hemorrhages increased in both eyes.
5	F.C.	51 F.	20	130/80	100	18	Good 25 U	Moderate	15 mg. - 3 mos. 60 mg. - 8 mos. 75 mg. - 12 mos 150 mg. - 3 mos. 300 mg. - 6 mos.	32	Pre-retinal hemorrhages appeared. Some absorbed while others extended into vitreous, forming bands of retinitis proliferans
6	R.B.	28 F.	15	140/90	0	0	Good 35 U	Moderate	30 mg. - 2 mos 100 mg. - 3 mos. 200 mg. - 7 mos.	12	More hemorrhages appeared
7	V.G.	60 F.	1 2	150/80	0	120	Good 26 U	Moderate	15 mg. - 11 mos 150 mg. - 5 mos.	16	No apparent change in retinal hemorrhages
8	L.B.	48 F.	4	150/80	0	0	Good	Early	30 mg. - 4 mos. 100 mg. - 5 mos. 200 mg. - 3 mos.	12	No retinal hemorrhages developed in right eye. Retinal hemorrhage in left eye persisted
9	C.N.	63 F.	10	160/60	45	64	Fair 30 U	Early	5 mg. - 3 mos 10 mg. - 4 mos. 75 mg. - 11 mos. 100 mg. - 4 mos.	21	Cataract in right eye Retinal hemorrhages in left eye persisted No fresh hemorrhages appeared.
10	J.M.	57 M.	5	160/100	45	0	Good 20 U	Moderate	25 mg. 2 mos. 30 mg. 1 mo. 150 mg. - 4 mos 100 mg. - 6 mos	13	No apparent change in retinal hemorrhages.
11	N.M.	47 F.	1	160/90	N	N	Fair 40 U	Early	200 mg. - 6 mos 100 mg. - 1 mo.	7	Punctate hemorrhages did not absorb No fresh hemorrhages appeared
12	L.J	60 F.	8	190/105	32	20	Good 10 U	Early	40 mg. - 7 mos. No treatment - 7 mos 100 mg. - 4 mos	11	Hemorrhages absorbed and H.M.C was stopped Punctate hemorrhages reappeared and absorbed again after H.M.C was given
13	L.G.	62 F	2	140/80	56	0	Good 20 U	Moderate	100 mg. - 1 mo 200 mg. - 4 mos.	5	Punctate hemorrhage and cotton wool exudate in left eye absorbed
14	A.D.	66 F.	12	150/90	150	150	Good 15 U	Moderate	90 mg. - 2 mos 150 mg. - 2 mos	4	Absorption of some hemorrhages in both eyes
15	T.T.	49 F.	15	130/80	N	N	Good 35 U.	Moderate	100 mg. - 5 mos 200 mg. - 6 mos.	11	Absorption of cotton wool exudates and some hemorrhages in both eyes
16	L.M.	33 F.	6	140/80	N	N	Poor 70 U	Moderate	15 mg. - 2 mos. 30 mg. - 2 mos. 60 mg. - 1 mo. 150 mg. - 3 mos 200 mg. - 2 mos.	10	Many hemorrhages absorbed when dosage of H.M.C was increased to 150 mg. daily
17	G.B.	40 F.	21	150/80	66	20	Fair 35 U	Early	15 mg. - 1 mo. 50 mg. - 4 mos. No treatment - 7 mos. 15 mg. - 2 mos. 75 mg. - 2 mos. 150 mg. - 2 mos.	11	Hemorrhages absorbed and H.M.C was stopped Hemorrhages reappeared and persisted after H.M.C was given again.
18	N.R.	74 M.	7	140/80	N	N	Good 30 U	Moderate	15 mg. - 16 mos. 100 mg. - 5 mos. 200 mg. - 6 mos.	27	Hemorrhages and waxy exudates increased in right eye Hemorrhages increased in left eye but began to absorb when dosage was increased to 200 mg daily
19	E.R.	30 F.	16	110/70	50	8	Fair 15 U	Early	20 mg. - 7 mos 40 mg. - 14 mos 200 mg - 2 mos 100 mg. - 2 mos.	25	Hemorrhages increased but some absorbed after daily dose was increased to 200 mg
20	W.R.	73 M.	10	140/70	N	N	Good 42 U	Early	15 mg - 12 mos. 200 mg. - 4 mos	16	Punctate hemorrhages absorbed and and fresh ones appeared.
21	A.Y.	48 F.	1	155/90	N	N	Good 34 U	Moderate	150 mg - 7 mos. 100 mg - 3 mos No treatment - 10 mos 100 mg. - 1 mo. 150 mg. - 4 mos.	15	H.M.C was stopped after hemorrhages began to absorb When hemorrhages reappeared treatment was started again without effect
22	M.C	54 F.	14	180/100	20	N	Poor 50 U	Moderate	150 mg. - 27 mos	27	No apparent change for 2 years Then hemorrhages appeared to be absorbing

orrhages is known to occur.

In 6 patients (Cases 17 to 22) there was no correlation between the administration of hesperidin methyl chalcone and the absorption of hemorrhages. In Cases 17 and 21, where the patient was used as his own control, improvement could not be duplicated when hemorrhages reappeared after administration of the drug was discontinued. Case 20 showed absorption of pin-point hemorrhages temporal to the disk, but while still receiving treatment a light shower of punctate hemorrhages appeared around the macula.

Using the capillary fragility test as an index of capillary integrity, 9 patients were found to be normal. Of the 18 having increased capillary fragility, 9 showed improvement, 2 were unchanged, and 2 became worse after taking hesperidin methyl chalcone. There were 3 patients (Cases 2, 3, and 5) whose retinopathy increased even though there was a marked reduction in their capillary fragility.

Discussion. There is good evidence that diabetes does affect capillaries. Ballantyne[2] has demonstrated the presence of retinal capillary aneurysms which he regards as the earliest sign of diabetes in the fundus. The aneurysms resemble punctate hemorrhages, but can be differentiated from them with the ophthalmoscope. Friedenwald[4] has shown that in some cases the aneurysm may be incompletely lined by endothelium and suggests that the initial process may be a break in the capillary wall through which blood escapes forming a punctate hemorrhage. The red cells may then be enveloped by endothelial cells forming a minute saccular aneurysm. Hanum[6] reported that diabetics with hemorrhagic retinopathy showed increased capillary fragility. Other investigators have also been able to demonstrate that capillary fragility is greater in diabetics with hemorrhagic retinal lesions than in diabetics who do not show a retinopathy.

The process by which diabetes damages capillaries is still unknown. Whether the damage causes increased capillary fragility or permeability or both also remains undetermined. Therapeutic use of vitamin P in retinal hemorrhages is based on the concept that this vitamin is an important factor in maintaining normal capillary permeability. McLean[11] reported improvement in 2 diabetics who received dicumarol and rutin. Shanno, *et al.*[17] studied a group of patients with diabetic retinopathy who received 60 mg. rutin daily. They could not reach definite conclusions but suggest that rutin might prevent further retinal hemorrhages.

If the concept that diabetes injures capillaries, thereby causing retinal hemorrhages, is valid; then any therapy which improves or restores the integrity of the capillary wall should prevent further hemorrhages and probably aid in the absorption of those already present. Since almost 70% of the patients with abnormal petechial indices were improved, it would seem reasonable to attribute the improvement in capillary permeability or fragility to the administration of hesperidin methyl chalcone. However, the improved state of the capillaries as indicated by fragility tests was not reflected by corresponding improvement in retinal hemorrhages and this is the most important consideration.

There were 6 patients (Cases 1 to 6) who showed a definite increase in the number of hemorrhages. In another group (Cases 17 to 22) there was no definite correlation between therapy and the course of the retinopathy. Some hemorrhages absorbed while fresh ones appeared. These 12 patients presented a progressive change in retinal lesions which was apparently not influenced by taking hesperidin methyl chalcone. In 5 patients (Cases 7 to 11) the retinopathy remained stationary and in these instances the administra-

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tion of hesperidin methyl chalcone may have prevented any fresh retinal lesions from appearing. Where there was evidence of improvement (Cases 11 to 17), hesperidin methyl chalcone may have played some part in the absorption of retinal hemorrhages. It should be emphasized again that the retinopathy of diabetes does show spontaneous changes.

Conclusions. A group of diabetic patients was studied to determine the effect of vitamin P on diabetic retinopathy. As part of the study prothrombin time and capillary fragility were measured. The level of plasma proteins was also determined. Although the number of patients observed over a sufficiently long period was not large, the following conclusions seem justified.

1. There was no significant alteration in the plasma albumin or globulin of 23 diabetics. All but 3 had some evidence of diabetic changes in the retina.

2. The prothrombin time tended to increase in those patients whose known duration of the disease averaged 10 years. As would be expected these patients also showed more extensive changes in the retina. The relationship, if any, between prothrombin time and diabetic retinopathy deserves further study.

3. About 50% of the cases of retinopathy in this group displayed increased capillary permeability, as manifested by the petechial index. There did not appear to be any correlation between capillary permeability and prothrombin time.

4. The petechial index improves in many cases after the administration of vitamin P, suggesting that this vitamin has some effect on capillaries. In most patients where this was observed there was no significant alteration in the appearance of retinal hemorrhages. Retinal hemorrhages are seen in diabetics who do not show increased capillary fragility.

5. Vitamin P did not alter the course of diabetic retinopathy in a majority of these cases. There were 6 whose lesions progressed, 5 who showed improvement, while 5 others have benefited, since no fresh lesions appeared. Any favorable effect attributed to vitamin P must take into consideration the possibility of spontaneous changes in retinal lesions of diabetes.

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THE ELECTROCARDIOGRAM IN MYOCARDIAL INFARCTION: ITS VALUE AS A DIAGNOSTIC AID IN 130 AUTOPSIED CASES*

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The electrocardiogram has been recognized as an aid in the diagnosis of myocardial infarction for almost 30 years. During this period there have been numerous reported instances and countless unreported cases in which diagnosis was established during life by the electrocardiogram and later confirmed at autopsy. There have been many other instances—less often reported—in which an electrocardiographic diagnosis of myocardial infarction was not confirmed at subsequent autopsy. There have, however, been surprisingly few reports evaluating the electrocardiographic diagnosis of myocardial infarction in a large series of consecutive cases.[1,5,6,7,8,12] It is the purpose of this article to report the electrocardiographic findings in a considerable group of cases of myocardial infarction and to evaluate the electrocardiogram in the diagnosis of this disease.

Method: Cases used in this study were those that died and were autopsied at this hospital during the 3 year period from April 1, 1945 to April 1, 1948. These cases fall into 2 groups, the first group being composed of all patients autopsied during the 3 year period on whom there was a pathological diagnosis of myocardial infarction. The second group is composed of those cases on whom a clinical diagnosis of myocardial infarction was made positively or was considered first among multiple diagnoses and on whom subsequent pathological study failed to confirm the diagnosis. (This study is concerned with infarctions of the ventricular myocardium only. Infarctions of the auricles were not noted or recorded in review of the autopsy data, and in this article the term "myocardial infarct" refers to infarcts of the ventricles only.)

In the vast majority of these cases no special sectioning or injection techniques were employed. The autopsy diagnosis of myocardial infarction was made in most instances by observation of the gross specimen with subsequent confirmatory microscopic study. In a few instances of very early infarction only microscopic myocardial changes were present when a coronary occlusion was apparent on gross examination. With one exception all of the cases of myocardial infarction included in this series showed infarcts at least 1 cm. in diameter, and the many cases showing multiple microscopic infarcts or small fibrotic patches were excluded from the group judged to show infarcts. Similarly cases showing only very small infarcts seen only on microscopic study were included among the cases that were considered not to show infarcts, and it is recognized that by routine methods similar infarcts may completely escape observation. By this means it was hoped to restrict the cases included to those infarcts that could reasonably be supposed to be diagnosed by ECG study. Unless otherwise described all infarcts extended through a full thickness of ventricular wall.

The ECG policy employed at this hospital during the period covered by this study may be briefly summarized. Routine ECGs taken on patients hospitalized included the 3 "standard" leads (I, II, and III) and an additional single chest lead taken with the exploring electrode at position 4. This lead was usually CF4, occasionally V4.

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TABLE 1. PATIENTS WITH PROVED ANTERIOR MYOCARDIAL INFARCTS ON WHOM ONE OR MORE ECGs WERE TAKEN.

Case No.	History suggesting acute coronary disease	No. of leads taken	ECG diagnosis	ECG data	Kind of infarct found
			RECENT INFARCTS		
5	Pos.	4	Left vent. preponderance.	In CF4; doubtful Q wave, ST segment up 1-2 mm., doubtful T wave inversion.	Large early ant.
10	Neg.	4, 4	Sinus tachycardia.	In second CF4, small Q, small jagged R, then deep S. No segment shift, T inversion.	Large early ant.
11	Pos.	4	A-V block, RBBB.	In CF4, ST segment up 2 mm., beginning inversion of T.	Rec. ant. 3 cm. in diam.
12	Neg.	4, 4	Vent. tachycardia.	Vent. tachycardia on first record. Diphasic T in leads II and CF4 on second record.	Rec. high ant.-septal 3 cm. in diam.
18	Pos.	12, 4	Ant. infarct.	Multiple precordial leads showed small R waves, deep S, ST segment up 2 mm. with T starting to invert. Later same day CF4 showed Q.	Massive ant.
19	Pos.	4, 4	Ant. infarct.	In CF4, small R, deep S, ST slightly elevated, T inverted.	Large ant.
21	Neg.	4, 4	Ant. infarct.	In CF4, small R, deep S, ST slightly elevated, T inverted.	Rec. large ant. and septal.
23	Pos.	4	Runs of vent. tachycardia, RBBB.	Same. No specific changes of infarction.	Red. and old near apex, 4 cm. in diam.
24	Pos.	4, 12	Ant. infarct. Left BBB.	In CF4, small R, elevated ST segment, inverted T. Second ECG showed LBBB.	Large ac. ant.
30	Pos.	4, 4	Ant. infarct.	In CF4, large Q, elevated ST, inverted T. Inverted T also in leads I, II.	4 x 6 cm. ac. ant.
34	Pos.	4	Ant. infarct.	In CF4, large Q, elevated ST inverted T.	Rec. ant. 3 cm. in diam.
38	Pos.	4, 4	Complete A-V dissociation.	In both ECG's CF4 showed R almost absent, elevated ST, inverted T. Also RBBB.	Large ac. ant.
39	Neg.	4, 4	Aur. fibrillation.	Aur. fibrillation. Inverted T in CF4. Otherwise normal.	Rec. sub-endocardial (at apex, 1 cm. in diam.).
51	Neg.	4, 4	Wolff-Parkinson-White type BBB.	Same. No evidence of infarction changes.	Rec. ant. apical 4 cm. in diam.
52	Neg.	4	Aur. fibrillation.	R small or absent in CF4. No ST or T change. Low T in lead I.	Rec. ant. 2 cm. in diam.
53	Pos.	4, 4, 12, 4	LBBB(x3). Ant. infarct.	First 3 ECG's showed LBBB. Last showed Q wave, elevated ST, inverting T in CF4.	Ant. septal 3 cm. in diam.
68	Pos.	9	RBBB, ant. infarct.	Large Q in CF1 through 6 with ST elevated 1 to 5 mm.	Large ac. ant.
72	Neg.	4	Aur. fibrillation, right axis deviation, digitalis effect.	Same. No evidence of infarction.	Rec. ant. 3 cm. in diam.
73	Pos.	12	Ant. infarct, RBBB.	Elevated ST, inverted T in leads V1, V2, V3, aV1 but not in lead I. No Q.	Acute ant. septal 3 cm. in diam.
75*	Pos.	4	Ant. infarct.	Large Q, elevated ST in CF4. No T wave inversion.	Old, large ant.
79	Pos.	4	Somatic tremor	Same. No changes demonstrating infarction.	Acute apical, 3 cm. in diam.
87	Neg.	4, 4	"Non-specific abnormal record."	Same. No changes demonstrating infarction.	Large ac. ant.
88	Pos.	4	Ant. infarct.	CF4 showed large Q, ST elevated 3 mm.	Large ac. ant.
89	Pos.	4	Ant. infarct.	Small R wave, ST elevated 5 mm., T wave inverting in CF4.	Large ac. ant.
90	Neg.	4, 4, 4, 4	Left vent. preponderance.	Same. No changes demonstrating infarction.	Rec. ant. septal 1 x 3 cm. in area.
96	Pos.	4	Left vent. preponderance.	Same. No changes demonstrating infarction.	Rec. large ant.
98**	Pos.	4, 4, 4	Ant. infarct.	Large Q, elevated ST, inverted T in CF4 in every instance.	Large ant. aneurysm, no infarct.
			OLD INFARCTS		
41	Neg.	4	Left vent. preponderance.	In CF4 wide but shallow Q, no ST or T change.	Old ant. at apex, 2 x 4 cm.
46	Neg.	4	Left vent. preponderance.	ECG not available.	Old apical, 3 cm. in diam.
86	Neg.	4	"Abnormal record."	Flat T wave in CF4 is only abnormality.	Old apical, 2 x 3 cm.
97	Neg.	4, 4, 12, 4	Left vent. preponderance (x2). Ant. infarct (x2).	Q waves in V1 through V4. ST elevated and T inverted in V3 and V4.	Old, large ant.-septal.

* Case 75 in hospital twice for myocardial infarction.

** Case 98 in hospital twice, once for infarction.

When additional leads were thought to be indicated (either by the clinicians or by the electrocardiographer) these were taken either as part of the initial ECG or in subsequent tracings. The additional leads most frequently taken were multiple chest leads with the exploring electrode placed in the 6 positions commonly used today and the 3 unipolar extremity leads.[3,11,13] Other chest and unipolar leads were taken infrequently and irregularly, so that in this study they have neither been reported nor analyzed. Usually ECGs taken as emergencies were read first by residents on the wards who were familiar with patients' clinical findings. All ECGs were subsequently seen by a junior resident assigned to the ECG service and again by one or more of four staff men each of whom has had several years' experience in clinical cardiology and ECG interpretation. Electrocardiographers were as a rule not familiar with patients' clinical findings and history. In consequence, ECGs were read initially without the availability of clinical information but were checked later against a brief clinical note on the ECG request ship. Since ECGs once read were sent to the wards and bound with patients' charts, they were usually not examined by the electrocardiographers when serial tracings were taken, although a note of previous ECG findings frequently accompanied requests for subsequent tracings.

In reviewing cases in this study the procedure employed was as follows: After pathological reports, charts, and ECGs on all patients were assembled, a patient's ECG was first examined by the author and tentative diagnosis made. This was then checked with the official hospital ECG diagnosis, then with the patient's clinical chart, and finally with the autopsy report. In cases where there was apparent disparity among any of these reports or when the author had previous familiarity with any aspect of the case, the material was reviewed by one or more of the staff electrocardiagraphers. By this means it was hoped that analysis of the data would be made impartially and that initial ECG interpretations would be uninfluenced by knowledge of clinical or pathological data.

The system employed by the hospital in coding charts and the system for filing ECGs undoubtedly excluded several cases that would ideally have been included in this study. These cases are in the main those on which on ECG diagnosis of myocardial infarction was made several months before the patients' death, and not confirmed at autopsy. Since cases were collected initially through the pathology department rather than from the ECG files or the record room, it is probable that several cases were excluded because myocardial infarction was not mentioned in the death note diagnosis or found at autopsy, although the diagnosis might have been made in some earlier ECG reading.

Results: *A. Cases with myocardial infarction proved at autopsy.* In this group were 100 cases having an average age of 63.3 years. This included a range from 15 to 90 years, the youngest patient being a colored male with infarction resulting from a luetic ostial occlusion. These 100 cases included 67 males and 33 females; 87 patients were white and 13 colored. In the entire group 45 cases were either never studied electrocardiographically or had ECGs taken at a time which review of all data suggested was prior to the development of myocardial infarction.

Among the 100 cases of proved myocardial infarction, 55 were studied with one or more ECGs taken at times when they should be expected to record the changes produced by myocardial infarction. The data from these cases are presented in Tables 1, 2, and 3. One of these cases (Case 75) was hospitalized twice with a diagnosis of myocardial infarction and so is listed twice in the tables. In these tables the notation "4 leads" means that 3 standard leads and a CF or V4 lead were taken, "9 leads" means that 6 precordial leads were taken in addition to the 3 standard leads, and "12 leads" means that 3 standard leads, 6 precordials, and 3 unipolar extremity leads

employing the Goldberger technique were taken.

The data in these tables have been grouped according to the site of the infarct demonstrated at autopsy. Referring first to the acute infarcts on the anterior surface of the heart (Table 1) it may be seen that there were 27 of these. Of these 27, 13 (48%) were diagnosed electrocardiographically. Review of the ECG findings and correlation with pathological data reveals no instance in which the ECG changes that were attributed to the infarction might reasonably be supposed to arise from some other cause. Of the total group of 27 cases, 9 had no recorded history suggesting acute coronary disease. None of these 9 cases was studied by more than the minimal 4 leads. An ECG diagnosis of infarct was made in only 1 (11%) of these 9 cases. Review readings of the ECGs in these cases show 2 additional instances (Cases 10 and 52) in which changes in CF4 were probably due to the underlying infarct.

Of the 18 anterior infarct cases with a history positive for acute coronary disease 12 (67%) were diagnosed elec-

TABLE 2. PATIENTS WITH PROVED POSTERIOR MYOCARDIAL INFARCTS ON WHOM ONE OR MORE ECGS WERE TAKEN

Case No.	History suggesting acute coronary disease	No. of leads taken	ECG diagnosis	ECG data	Kind of infarct found
			RECENT INFARCTS		
9	Pos.	12	Post. infarct.	Lead III of small voltage composed of Q or QS 2 mm. deep and .04 sec. wide; aVf composed of small R, no Q; ST depressed 3 mm. in V3 and V4.	Rec. large post. near septum.
14	Pos.	9	Post. infarct.	Large Q3 with inverted T wave. Precordial leads not remarkable.	Rec. post. near septum, 3 x 4 cm. in area.
15	Neg.	12, 12	Post. infarct.	Large Q3 with inverted T wave. Height of R wave in aVf diminished in progressive ECG's.	Rec. post. 3 cm. in diam.
18	Pos.	4	Post. infarct.	ECG not available.	Ac. post. 3 cm. in diam.
20	Neg.	I, II, III, CF_2, CF_4, CF_6	Sinus tachycardia.	Sinus tachycardia. Large Q2 and Q3 without ST or T wave change. Precordial leads not remarkable.	Rec. 4 x 4 cm. post.
33	Pos.	4, 4	Post. infarct.	Large Q2 and Q3 with ST segments greatly elevated.	Rec. large post.
63	Pos.	4	Post. infarct.	Large Q2 and Q3 with ST segments greatly elevated and T waves inverting.	Rec. post. 3 cm. in diam. near septum.
66	Neg.	4	Ant. infarct.	No ECG change specifically attributable to infarction in leads II or III. CF4 showed very small R, ST elevated 2 mm., absent T.	Rec. post. 3 x 4 cm.
75*	Pos.	4	Post. infarct.	Q2 and Q3 present with ST elevated 2 mm. and T wave inverting. Changes of previous anterior infarct seen in CF4.	Rec. large post. near septum.
77	Pos.	12	Post. infarct.	Q wave present in II, III, aVf with ST elevated 1 mm. V3 and V4 showed R wave almost absent with ST segment elevated 4 mm.	Rec. 3 x 4 cm. post. at septum near apex.
80	Pos.	4	"Abnormal record."	Large Q3 with no ST shift and upright T wave.	Rec. post. 0.5 x 1 mm. high, near septum.
83**	Pos.	4, 4, 12	Post. infarct, Compl. A-V block.	ST elevation, T wave inversion in II, III, aVf. No Q waves. Compl. A-V block.	Old post. 3 cm. in diam. near septum.
95	Pos.	12, 4, 4	Compl. A-V block, RBBB.	Large Q in II, III, aVf with deeply inverted T wave. Precordials showed RBBB.	Large rec. post.
			OLD INFARCTS		
7	Neg.	4	"Abnormal record."	Low voltage in all standard leads. No changes demonstrating infarction.	Old 3 x 4 cm. post. near septum.
99	Neg.	4	"Abnormal record."	No changes demonstrating infarction.	Old post. 4 cm. in diam.

* Case 75 in hospital twice for myocardial infarction.

** Case 83 in hospital twice, once for infarction.

trocardiographically. Five of these cases were studied with complete precordial leads, and in all of these cases the infarct was diagnosed by ECG. Review of the tracings on these 5 cases shows only 1 case (Case 73) in which a precordial lead at position 4 should not have suggested the diagnosis.

Of the remaining 13 cases with positive histories but without multiple precordial leads the ECG diagnosis was made in 7 cases (54%). Review readings of the ECGs in these cases show 3 additional instances (Cases 5, 11, 38) in which changes in CF4 were probably due to the underlying infarct. Of the total group of acute anterior infarcts studied with only 4 leads, 8 of 22 (36%) were diagnosed by ECG. This contrasts with 5 of 5 (100%) studied with multiple precordial leads.

Of the 4 cases having infarcts classified as "old" occurring on the anterior surface of the heart 1 (25%) was diagnosed by ECG. None of these cases had a history suggesting coronary disease. The one case in which the diagnosis was made electrocardiographically was diagnosed from a 12 lead ECG. Review of this and the other ECGs taken on this patient reveals changes in the isolated lead 4 which are definitely attributable to the infarct. The diagnosis, however, was made only when the 12 lead ECG was taken. The remaining 3 cases in this group were studied only with the 4 lead ECG. Of these 3 cases review shows changes in lead 4 of 1 case which should have suggested infarction. In a second case the ECGs were not available for review, and in the third case there are no ECG changes which can be attributed definitely to infarction.

There were 13 cases in which pathological study showed posterior infarcts that were classified as acute (See Table 2). Of these 13 cases, 9 (69%) were diagnosed electrocardiographically. Of these 13 cases 3 had no recorded history of coronary disease, and in these 3 cases the ECG diagnosis was correct in 1 and incorrect in 2. One of the incorrect diagnoses (Case 66) was called an anterior infarct, so that while for clinical purposes the diagnosis can be considered correct, electrocardiographically it is not accurate. The one case with correct ECG diagnosis among these 3 was the only one studied with 12 leads.

Of the 10 cases of acute posterior infarction with histories positive for coronary disease the ECG diagnosis was made in 8 (80%). Six of these cases were studied with no more than 4 leads and with 5 correct ECG diagnoses. Four were studied with 12 leads with 3 correct ECG diagnoses. In the entire group of 13 cases, 5 of 8 (63%) correct ECG diagnoses were made when 4 leads were used and 4 of 5 (80%) when 12 leads were used.

Of the 2 cases of posterior infarction classified as "old," both were studied with 4 lead ECGs only. Neither had a history positive for coronary disease, and neither was diagnosed electrocardiographically.

The remaining cases of proved infarction (Table 3) are too few for any statistical analysis to be attempted. High lateral infarcts are grouped separately because of the special problems involved in their ECG diagnosis.[10] The 3 cases in the group of multiple infarcts are not well classified elsewhere. The cases of isolated right ventricular infarcts, left bundle-branch block, and ventricular tachycardia are grouped separately because infarcts in these categories are generally considered impossible of diagnosis by electrocardiographic means.

B. Cases with myocardial infarction not proved at autopsy. In this group were 30 cases having an average age of 58.3 years. This included a range from 29 to 78 years. In this group

of patients were 26 males (86%) and 4 females (14%); 24 (83%) were white and 6 (17%) were colored. These cases represented patients dying of a fairly wide variety of diseases. Most of them were hospitalized for relatively short periods of time or died suddenly and unexpectedly while in the hospital. The common factor among them is that in every instance a final clinical diagnosis of myocardial infarction was stated positively or was regarded as a probable first choice among several possibilities. In none of these cases was the diagnosis of myocardial infarction substantiated by post mortem examination.

The data on these cases are tabulated in Table 4. It may be noted that of the total of 30 cases 14 were not studied by any ECG that was pertinent to the terminal event. In the remaining 16 the ECG was not read as suggestive of infarction in 10 cases but was read as such in 6 cases. The itemized presentation of these 6 cases shows that in 3 instances a clinical diagnosis of myocardial infarction was not made or considered probable until it was influenced by an ECG diagnosis of infarction. In the other 3 cases an ECG diagnosis of infarct tended to confirm an already erroneous diagnosis.

Discussion: A study such as this one which is based on the collection of a number of hospital cases, many representing patients who were not the objects of special study during life, must of course raise problems which are not answered. From the review of material on the 100 cases of proved myocardial infarction several observations are suggested. The first of these is that of the total number of patients with myocardial infarcts only about half (55%) will receive an ECG study at such a time that their infarction can be demonstrated electrocardiographically. This percentage could undoubtedly be increased without great change in current hospital procedure; but for the figure to approach 100% it would seem necessary to make an ECG study almost a routine procedure on all patients or at least all beyond early adult life.

Of the 55 patients (56 cases) with myocardial infarction there were 2 who showed left bundle-branch block in all ECGs taken and 1 with ventricular tachycardia. This amounts to about 5% of all cases, and in these cases the ECG can be of no positive help in regard to infarcts, as the changes produced by left bundle-branch block and ventricular tachycardia, according to contemporary electrocardiographic theory, will completely obscure those resulting from infarction of the ventricles.[14] Similarly isolated right ventricular infarcts are not thought to be amenable to specific ECG diagnosis. In this series there were 2 of these infarcts. Although 1 (Case 40, Table 3) was diagnosed on the ECG, its localization was not correct. For the purposes of this study these should probably be included in the group of those which cannot be diagnosed electrocardiographically.* Added to the cases just mentioned, this would bring up to 9% the number of cases in which the ECG was of no specific diagnostic aid.

Among the total of 56 cases there were 29 (52%) diagnoses of myocardial infarction including as correct diagnoses the few cases in which the localization of the infarct was obviously erroneous. Among the cases with a history positive for coronary disease the figure was 24 in 33 (73%). Among the cases with a negative history there

* The author can find no clear statement in the literature as to electrocardiographic correlation with infarcts of the right ventricle. However, the relative electrical positivity of the interior of the right ventricle during the early part of the QRS complex in the normal heart theoretically prevents the development of a Q wave in isolated infarction of the right ventricle.

were 5 diagnoses in 23 cases (22%). The reasons for this disparity would appear to depend chiefly on the following factors: the size of the infarct, the frequency in the use of multiple leads beyond the minimal 4, and the degree of influence that a positive history may have on the individual making the ECG interpretations.

TABLE 3. MISCELLANEOUS PROVED MYOCARDIAL INFARCTS

Case No.	History suggesting acute coronary disease	No. of leads taken	ECG diagnosis	ECG data	Kind of infarct found
			HIGH LATERAL INFARCTS		
62	Pos.	I, II, III, CF_2, CF_4, CF_6	Ant. infarct.	In CF4 very narrow Q 3 mm. deep; inverted T wave. In standard leads no changes demonstrating infarction.	Rec. high post.-lat. 3 cm. in diam.
100	Pos.	4, 12	High ant.-lat. infarct.	First ECG non-contributory. Second showed small Q in I, V6, large Q with inverted T wave in aVl.	Rec. high post.-lat. 4 cm. in diam.
			MULTIPLE INFARCTS		
16	Neg.	4	"Abnormal record."	Low voltage in standard leads. CF4 showed nor. R, deep S wave.	Old large ant.-septal, rec. large high post.-lat.
74	Pos.	4, 4, 12	Post. and septal infarct.	Large Q2 and Q3 with inverted T waves. Large Q in V1, V2, V3.	Of entire intervent. septum with perf.
94	Neg.	4	Post. infarct.	Low voltage lead III with small Q wave; sl. T wave inversion.	Many small; of entire Intervent. septum.
			RIGHT VENTRICULAR INFARCTS		
8	Neg.	4	Digitalis effect.	Same. No changes demonstrating infarction.	Old post. of right vent., 2 x 4 cm. in area.
40	Pos.	4	Post. infarct.	ST2 and 3 elevated 1 mm.; early inversion of T waves in these leads.	Early ant. of right vent. 2 x 3 cm. in area.
			ELECTROCARDIOGRAMS SHOWING LEFT BBB ONLY		
6	Pos.	4, 4	Left BBB.	Same.	Old and rec. ant.
50	Neg.	4, 4, 4	Left BBB.	Same.	Old and rec. post.
			ELECTROCARDIOGRAMS SHOWING VENTRICULAR TACHYCARDIA ONLY		
31	Neg.	4, 4, 4, 4	Vent. tachycardia.	Same.	Old large ant. vent. aneurysm. No infarct.

The pathology reports used in this study did not always have recorded the exact measurements of the infarcts described, so that no specific conclusions can be drawn as to exact size. Rough observation of the data in this report shows no apparent correlation between the size of the infarct and the presence of a history suggestive of infarction. Review of other literature on myocardial infarction confirms this observation.[2] Among the cases described in this report multiple chest leads and unipolar extremity leads were more often taken when clinical findings suggested the presence of infarction, and as has been shown these made a considerable contribution in establishing the diagnosis by ECG. The subjective element is more difficult to evaluate. As described earlier, the ECG policy employed at this hospital is planned so as to eliminate as far as possible the influence of clinical data on the initial ECG reading. It is difficult to believe, however, that this influence is completely eliminated. As an example, it is difficult to imagine how an individual could be confronted with a 12 lead emergency ECG and not search carefully for indications of myocardial infarction.

The percentage of correct ECG diagnoses in anterior infarcts (48% in acute cases, 45% in all) is considerably inferior to the percentage in posterior infarcts (69% in acute cases, 60% in all). The 100% of correct diagnoses in cases of anterior infarction where 6 precordial

leads were taken suggests that anterior infarcts are much more frequently diagnosed by this technique. There were only 6 cases in this group. They may have been in some measure selected cases from a clinical standpoint, and review of the ECGs indicates that some of these cases should have been diagnosed from a precordial lead taken at position 4 alone. By way of contrast, however, are the 2 cases showing changes in isolated CF4 leads almost certainly due to infarction which were missed on the initial reading. There are in addition a few other cases where changes in the single precordial lead are probably due to infarction, and there are also several cases in which very large anterior infarcts found at autopsy were missed by a single precordial lead where there is every reason to suppose that multiple leads would have shown changes due to infarction. An additional factor in this regard is the variability in placing of the precordial electrode. In obese patients and in patients with chest deformities due to emphysema it is frequently impossible to be sure of the relationship of the precordial electrode to the heart. The several examples in this paper of small R waves in lead CF4 almost without question include instances where the single precordial lead was placed more over the right ventricle than over the left. This is also illustrated by the cases in Table 4 which were misdiagnosed as anterior infarcts by virtue of small or absent R waves in CF4. It might also be mentioned that none of the proved cases of infarction in this series showed a type of precordial pattern that is so often read as suggestive of infarction. This pattern is that of absent R waves in the precordial leads taken at positions C1 and sometimes C2 with a progressive rise in the height of R as the electrode is moved over the left chest.

Contrasting with the situation seen in anterior or antero-lateral infarction the "posterior" surface of the heart, lying for the most part on the diaphragm, does not permit easy exploration with multiple leads. Esophageal leads are relatively impractical and difficult to apply, particularly in seriously ill patients. Multiple exploring leads

TABLE 4. INFARCTS DIAGNOSED CLINICALLY AND ELECTROCARDIOGRAPHICALLY WHICH WERE NOT FOUND AT AUTOPSY. SUMMARY OF CASES WITH POSITIVE DIAGNOSIS OF INFARCTS.

Case No.	History suggesting acute coronary disease	No. of leads taken	ECG diagnosis	ECG data	Autopsy findings
109	Neg.	4	Ant. infarct, left vent. prepond.	Very small R wave in CF4 with ST segment elevated 3 mm. and T wave inverting. Left vent. prepond. in standard leads.	Chr. passive cong. Mult. pul. infarcts.
110	Neg.	4, 4	Ant. infarct, left vent. prepond.	Absent R wave in first CF4, very small R wave in second. No ST shift. T waves upright. Left vent. prepond. in stand leads.	Perf. duodenal ulcer; peritonitis.
118	Neg.	4	Ant. infarct.	ECG not available.	Gangrene of lower esophagus.
127	Pos.	4, 12, 4	Post. infarct, nodal tachycardia.	Small Q wave in lead III but not in II or aVf. All records showed tachycardia, prob. nodal, poss. vent.	Chr. fibroid tuberc.
129	Pos.	4	Post. infarct.	Large Q3 with elevated ST segment and inverted T wave. Lead I: large S wave.	Widespread lobar pneumonia.
130*	Pos.	12	Ant. infarct.	Elevated ST segments in all precordials, lead I, lead aVl. No Q waves, no T wave inversion.	Hemoperic. due to ruptured aor. aneurysm.

* Case 130 is the same patient as case 83 in Table 2.

over the back, the subject of current reseach in several institutions, do not lend themselves to such easy interpretation as do leads over the anterior chest. By way of compensation, however, lead III is of considerably more value in diagnosing posterior infarcts than is lead I in anterior infarction. Similarly lead aVf is considerably more valuable than an isolated lead aVl. This point is aptly illustrated by the data in the tables, where the ECG patterns in leads I and aVl were so infrequently of diagnostic aid that they are tabulated in only a few cases.

In view of the difficulty in distinguishing the Q waves and inverted T waves of lead III caused by posterior infarction from those which are due to position alone it appears somewhat remarkable that such a high percentage of these cases were diagnosed correctly. It is quite probable that if our filing system had enabled the author to review all the ECGs upon which a diagnosis of posterior infarction had been based, several instances of erroneous diagnosis of posterior infarction would have been discovered which were missed because the patients died from other causes at a considerable time after this ECG diagnosis had been made. The small number of cases in Table 4, however, which were mistakenly called posterior infarction tends to discount this observation.

One aspect of the diagnosis of posterior infarction which seemed rather striking was the negligible value of lead aVf in differentiating "normal" from pathological Q waves in lead III. Recent studies, notably those of Goldberger[1] and of Myers and Oren,[2] have emphasized the value of this lead in the diagnosis of posterior infarction. It is true that of the 5 cases of posterior infarction in this study in which lead aVf was taken the diagnosis was made in 4 and that the fifth (Case 95, Table 2) represents perhaps the outstanding error of interpretation in all the cases presented here. Review of the tracings in these cases, however, shows no instance where the diagnosis was clearly presented in lead aVf but not seen equally well in lead III. The only exception to this statement might be provided by Case 15 (Table 2) where the height of the R wave in aVf diminished in progressive tracings.*

Another interesting aspect of the diagnosis of posterior infarction is seen in Cases 7, 66, and 99 of Table 2. These cases all had infarcts of moderate size, but in none of them were there any changes in lead III to suggest infarction. With the thought that perhaps extreme vertical position of the heart within the thoracic cavity coupled with clockwise rotation on the long axis might prevent these ECG changes from being referred to the diaphragm and the left leg the records on these cases were reviewed carefully. Chest films had been taken on two of the three cases, and review of these along with the recorded physical examinations and autopsy findings of all three cases showed no marked pulmonary lesion or chest deformity which might significantly shift the position of the heart within the chest.

* This rapid diminution in the height of an R wave in lead aVf—or for that matter in lead III—would appear to be a useful change to observe and one suggestive of posterior infarction. In the horizontally placed heart the foot electrode records the sum of the potential variations of the diaphragmatic surface of the heart. In the case of a small infarct of this surface or one so placed that its full electrical effect is not recorded by the foot electrode a Q wave may not appear on the tracing in lead aVf but the overall reduction in positive potential may reduce the height of the R wave in aVf. If before infarction the ECG of this heart showed an extremely small R wave in lead III due to position alone, the change in potential resulting from the infarct might be sufficient to cause a Q wave in lead III but not aVf. This Q3 is in a sense not the result of myocardial infarction but of infarction plus the effect of the heart's position within the chest. This apparently has occurred in this instance (Case 15, Table 2).

Of the 5 cases in which infarction was erroneously diagnosed by ECG and on which tracings were available for review (Table 4), 2 were clearly diagnosed on the basis of a small or absent R wave in a single precordial lead. In these cases multiple chest leads would almost certainly have clarified the picture sufficiently for a mistaken diagnosis of infarction to be avoided. One case was misread as a posterior infarct due to the presence of a large Q3 with elevated ST segment and inverted T wave. Review of this ECG shows it to be typical of posterior infarction in almost every respect except perhaps that it has a large S wave in lead I. It is possible that a lead aVf might have helped in making a correct diagnosis but the evidence presented earlier in this paper does not indicate that this is likely. Another case in this group was diagnosed wrongly as posterior infarct because of the distorting effect of a probable nodal tachycardia. The final case represents a pure error in interpretation, as review of the ECGs from this patient shows them to be typical of very acute pericarditis and not of acute infarction. In this entire study, which includes only autopsied patients, cases in which 6 precordial leads were taken were misdiagnosed electrocardiographically only through errors in interpretation and not because of insufficient data. The same might not necessarily be true in non-fatal disease.

Summary and Conclusions. 1. One hundred cases of proved myocardial infarction and 30 cases with a clinical diagnosis of myocardial infarction that was not found at autopsy are reviewed with special reference to the place of the electrocardiogram in the diagnosis of this disease.

2. Fifty-five patients with proved myocardial infarction were studied electrocardiographically at times subsequent to the development of their infarcts. In these patients myocardial infarction was diagnosed electrocardiographically in 52% of cases.

3. In 22 patients with proved recent anterior infarction the diagnosis was made electrocardiographically in 36% when only 4 leads were taken. In 5 patients with proved recent anterior infarction the diagnosis was made electrocardiographically in 100% when 6 precordial leads were taken.

4. In 8 patients with proved recent posterior infarction the diagnosis was made electrocardiographically in 63% when only 4 leads were taken. In 5 patients with proved recent posterior infarction the diagnosis was made electrocardiographically in 80% when unipolar extremity leads were taken in addition to these.

5. Sixteen patients with a clinical diagnosis of myocardial infarction were studied electrocardiographically. In 6 (38%) of these patients an incorrect electrocardiographic diagnosis of myocardial infarction was made, as infarction according to the criteria adopted was not found at autopsy.

6. Based on an analysis of these records, the use of 6 precordial leads as a routine procedure appears to be of great value in the accurate diagnosis of anterior myocardial infarction and represents a considerable improvement over the technique employing only a single precordial lead. When the multiple lead technique is used, errors in diagnosis will be almost exclusively those of electrocardiographic interpretation as contrasted with errors stemming from insufficient data.

7. The use of unipolar extremity leads appears to be of comparatively little value in the accurate diagnosis of myocardial infarction. Specifically the use of lead aVf appears to contribute little information toward the accurate diagnosis of posterior infarction.

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NEGATIVE RESULTS OF TOCOPHEROL THERAPY IN CARDIOVASCULAR DISEASE*

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For many years studies have been carried on in experimental animals to determine the metabolic function of vitamin E in relationship to the reproductive, muscular, and vascular systems. In the rat[1] it has been shown that vitamin E is necessary for reproduction. In the rat, guinea pig, rabbit and hamster, vitamin E deficient diets produce a profound alteration in the skeletal muscles microscopically similar to that found in the human muscular dystrophies.[2,3,6] It has been demonstrated that the oxygen consumption, creatine, and chloride content of muscles in vitamin E deficient animals may be influenced by feeding alpha tocopherol.[6] The clinical applications of these studies, however, have been disappointing. At one time enthusiasm was expressed over the possible value of vitamin E in the prevention of spontaneous and habitual abortion of unknown etiology in humans.[17] The more recent papers have described consistently negative results in the treatment of the muscular dystrophies with vitamin E.[5,9,11] There is ample evidence that the blood level of vitamin E can be raised with tocopherol therapy.[8,10,18] Although the germ of cereal grains and green leafy vegetables repre ents the richest natural sources of vitamin E, so universal is its distribution in the plant world that no one has as yet been able to devise a diet of natural foods suitable for the experimental production of vitamin E deficiency.[7]

A considerable number of animals have been observed to die suddenly while on vitamin E deficient diets.[4] One bovine which died suddenly was followed with serial electrocardiograms that showed gradual and progressive changes. Atrophy and scarring of cardiac muscle fibers were found to appear, along with an increase in the cellular elements. It was concluded that cardiac failure could be produced in cattle by means of a vitamin E deficient diet.

The reports[12,13,15,16] on the use of vitamin E in various types of heart disease with much attendant publicity have stimulated an interest in the possible therapeutic effects of this drug. Although there has been no critical study of the effects of large doses of vitimin E, an increasing number of patients have been seen by the authors in consultation who have been placed on vitamin E by their physicians.

The present study was undertaken in an attempt to evaluate by laboratory tests and clinical examinations the effect of tocopherol therapy in selected types of cardiovascular disease.

Procedure. In this study 7 patients with hypertensive vascular disease without cardiac enlargement by Roentgen-ray (Group 1), 7 patients with hypertensive vascular disease and cardiac enlargement by Roentgen-ray (Group 2), and 7 patients with classical and

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relatively stable angina pectoris (Group 3) were selected. The patients were seen usually at monthly intervals over periods of 5 to 20 months.

Each patient was given the benefit of a complete history and physical examination for purposes of classification. Electrocardiograms and 2 meter teleroentgenograms of the chest were taken along with blood plasma tocopherol levels to serve as controls. At each subsequent visit of the patient the pertinent interval history was recorded; a cardiovascular examination was performed; and the above laboratory data were repeated.

Medication in each instance was begun with oral placebos; each patient received initially placebos indistinguishable from the capsules containing tocopherol for 1 month. After 1 month of placebos, the patient was given tocopherol orally for 1 month. These 2 preparations were then alternated for periods of 1 month each throughout the period of observation. Purposely every patient was given the impression that he received the identical medication on each occasion.

During the earlier period of study, tocopherol therapy was begun with a daily dosage of 150 mg. of the mixed tocopherols. Later, tocopherol treatment was initiated at levels of 300 mg. daily of the alpha tocopherol. At subsequent visits the dosage of tocopherol was increased so that during the period of observation 13 patients received a daily dosage of 600 mg.; 2 patients received a daily dosage of 300 mg. of the alpha tocopherol for at least 1 or more months, and for 6 patients the maximum daily dosage was 150 mg. of the mixed tocopherols (See Table 1).

Results and Discussion. The results are summarized in Table 1. In every patient, it was found that the blood level could be raised significantly by the oral administration of tocopherol. In 21 instances of patients to whom 150 mg. per day of mixed tocopherols were administered for 1 month there was an average increase of 47% in the blood plasma tocopherol level (mean increase from 1.20 mg. per 100 cc. to 176 mg. per 100 cc., Table 2). There was an increase in the blood plasma tocopherol level in every instance, and the increment was thought to be significant in 20 of these.

In 11 instances of patients who received 300 mg. per day of alpha tocopherol for 1 month there was an average increase of 54% in the blood plasma tocopherol level (mean increase from 1.28 mg. per 100 cc. to 1.97 mg. per 100 cc., Table 2). There was a significant increase in 10 instances. There was some question whether the medication was taken in the 11th.

In 23 instances of patients who were given 600 mg. per day of alpha tocopherol for one month there was an average increase of 85% in the blood tocopherol level (mean increase from 1.59 mg. per 100 cc. to 2.95 mg. per 100 cc., Table 2). An increase in blood level was noted in every instance; in 22 the increase was thought to be significant.

In the hypertensive group without cardiac enlargement (Group 1), 2 patients felt generally better during the period of placebo therapy. This improvement was maintained throughout the period of study with alternating tocopherol and placebo therapy without significant change in blood pressure. In 2 patients the T-waves of the electrocardiogram became lower while on tocopherol therapy. One patient felt less well during tocopherol therapy. The remainder of the patients manifested no significant changes.

In the hypertensive group with cardiac enlargement (Group 2) 2 patients improved subjectively on placebo therapy but exhibited no objective changes. This improvement was maintained. Two patients with bundle branch block developed increasing enlargement of the heart; 1 of them progressed to congestive failure. No improvement was noted in the other patients of this group.

Of the 7 patients having angina, (Group 3) only 1 reported an increase in tolerance to exercise which began while receiving tocopherol. This improvement was sustained throughout the period of study. An additional patient improved while on placebos and maintained improvement throughout

TABLE 1.—ANALYSIS OF RESULTS OBTAINED

Case No	Age	Sex	Control: Mean B.P.	Control: Heart Size by X-ray	Control: Electrocardiogram	Control: Tocopherol Blood Plasma Level (mgm. %)	Tocopherol Therapy: Mean B.P.	Tocopherol Therapy: Heart Size by X-ray	Tocopherol Therapy: Electrocardiogram	Tocopherol Therapy: Maximum Daily Dosage (mgm.)	Tocopherol Therapy: Mean Tocopherol Blood Plasma Level (mgm. %)	Tocopherol Therapy: Range of Tocopherol Blood Plasma Levels (mgm. %)	Placebo Therapy: Range of Tocopherol Blood Plasma Levels (mgm. %)	Placebo Therapy: Mean B.P.	Months of Observation	Remarks
Group 1. Hypertensive Vascular Disease																
1	46	F	215/115	Upper limits of nor.	Nor.	1.53	233/135	N.C.*	N.C.*	150 mixed	1.84	1.63 - 2.09	1.22 - 1.45	220/123	13	Worse symptomatically on tocopherol.
2	51	F	166/114	Nor	Nor	1.59	165/110	N.C.*	N.C.*	600 alpha	2.40	2.06 - 2.81	1.07 - 1.70	172/110	10	N.C.I.[x]
3	53	F	210/110	Nor.	Nor	.94	196/115	N.C.*	$T_{1.2.3.}$ less	600 alpha	1.49	1.19 - 1.91	.89 - 1.17	199/121	13	N.C.I.[x]
4	65	M	170/110	Nor	Nor.	.67	169/105	N.C.*	N.C.*	600 alpha	1.92	1.37 - 2.83	.75 - 1.18	166/102	15	Improvement after placebos maintained throughout.
5	63	M	220/110	Nor.	Left axis deviation	1.77	163/94	N.C.*	T_1 less	600 alpha	2.44	2.23 - 2.73	1.48 - 1.93	175/96	8	N.C.I.[x]
6	50	F	210/110	Nor.	Nor.	1.19	179/100	N.C.*	N.C.*	600 alpha	2.66	1.64 - 3.98	1.07 - 1.51	176/102	11	After 1 mo. of placebos felt best in years. Improvement maintained.
7	41	M	180/112	Upper limits of nor	Nor.	1.44	197/116	N.C.*	N.C.*	150 mixed	2.11	2.04 - 2.17	1.47 - 1.55	205/116	7	N.C.I.[x]
Group 2. Hypertensive Vascular Disease with Cardiac Enlargement																
8	51	F	190/110	Enlarged	Left vent	1.32	200/112	N.C.*	N.C.*	150 mixed	1.99	1.86 - 2.02	1.22 - 1.26	192/118	9	N.C.I.[x]
9	54	F	190/110	S1. enlarged	Left axis deviation	1.31	155/87	N.C.*	L. a. dev. decreased to nor. limits	150 mixed	1.71	1.54 - 1.86	1.08 - 1.53	163/94	9	Improvement on placebos maintained. Lost 30 pounds on diet.
10	40	F	180/112	Enlarged	Borderline left axis deviation	1.37	163/97	N.C.*	No longer l. a. dev.	150 mixed	1.84	--	1.24 - 1.33	163/100	6	After 1 mo. of placebos less nervous and stronger. Impr. maintained.

11	77	F	264/116	Enlarged to left	Nor.	1.37	228/117	N.C.*	N.C.*	600 alpha	2.17	1.64 - 3.23	1.24 - 1.66	216/116	11	N.C.I.[x]
12	69	F	192/98	Sl. enlarged	Nor.	1.71	183/94	N.C.*	N.C.*	600 alpha	2.39	1.84 - 3.00	1.43 - 1.97	191/98	20	N.C.I.[x]
13	65	F	222/120	Enlarged to left	Left bundle branch block	1.25	188/103	Increasing	N.C.*	600 alpha	2.59	2.07 - 3.10	1.40 - 1.58	184/105	10	N.C.I.[x] Ht. progressive.
14	44	F	180/98	Nor.	Left bundle branch block	.69	161/92	Increasing	QRS interval incr. from .14 to .16 seconds	600 alpha	1.46	1.12 - 1.93	.66 - 1.02	162/93	17	Developed congestive heart failure on tocopherol.
Group 3. Angina Pectoris																
15	58	M	180/116	Enlarged	Left axis deviation	1.05	185/120	N.C.*	N.C.*	150 mixed	1.63	1.38 - 1.83	1.18 - 1.39	175/116	9	N.C.I.[x]
16	67	F	196/106	Enlarged	Left axis deviation	1.56	148/84	N.C.*	N.C.*	300 alpha	2.67	--	1.67 - 1.74	130/85	5	After 1 mo. of placebos improved. Lowered bl. pres. and less angina of effort. Impr. maintained on tocopherol.
17	57	M	120/76	Nor.	Long P-R Interval	.99	118/80	N.C.*	N.C.*	300 alpha	1.70	1.46 - 1.95	.93 - 1.19	115/84	6	Decrease in angina of effort during tocopherol therapy.
18	50	M	120/70	Nor.	Nor.	1.16	130/90	N.C.*	N.C.*	600 alpha	2.46	2.42 - 2.50	1.07 - 1.24	115/77	5	Increase in angina of effort during tocopherol therapy.
19	60	M	140/100	Enlarged	Nor.	1.12	160/110	N.C.*	N.C.*	600 alpha	2.76	2.16 - 3.36	1.75 - 1.82	133/90	7	Sense of wellbeing worse during tocopherol therapy.
20	57	F	170/100	Nor.	Nor.	2.01	175/105	N.C.*	N.C.*	600 alpha	4.56	4.46 - 4.69	2.01 - 2.82	165/100	5	N.C.I.[x]
21	58	F	210/94	Upper limits of normal	Nor.	1.32	218/110	N.C.*	N.C.*	600 alpha	2.66	1.72 - 4.53	1.28 - 1.62	207/92	17	N.C.I.[x]

*N.C. - No change.

[x]N.C.I. - No clinical improvement.

the follow-up period. One further patient became worse on tocopherol therapy. No change subjectively or objectively was noted in the remainder.

Thus it seems well demonstrated that tocopherol therapy produced no appreciable benefits in this group of patients. There was no significant improvement in symptomatology nor in objective findings. Specifically there was no lowering of the blood pressure, no decrease in heart size by Roentgenray, nor improvement in the electrocardiogram. The changes which were recorded indicating improvement in some and progression in others were no more than one might expect in the natural evolution of their cardiovascular disease. No toxicity from the drug was noted in any patient. There was no correlation between the level of blood plasma tocopherol and the clinical course of the patient. In patients with congestive heart failure we found that the tocopherol blood levels[14] were normal and not reduced.

Conclusion. In a series of 21 patients with cardiovascular disease followed from 5 to 20 months, tocopherol therapy was found to produce no appreciable benefit either subjectively or objectively.

The blood level of tocopherol can be significantly raised by the oral administration of the drug.

TABLE 2.—PLASMA TOCOPHEROL LEVELS AT VARIOUS STAGES OF THE STUDY.

No.	After 1 Month of Placebos	2 Months Later After 1 Month of 150 mg of Mixed Tocopherols Daily	3 Months Later After 1 Month on Placebos	After 1 Month of Placebos	2 Months Later After 1 Month of 300 mg of Alpha Tocopherol Daily	3 Months Later After 1 Month on Placebos	After 1 Month of Placebos	2 Months Later After 1 Month of 600 mg of Alpha Tocopherol Daily	3 Months Later After 1 Month on Placebos
1	1.24*	1.64	1.14	1.33	1.64	1.66	1.77	3.00	1.79
2	1.22	2.02	1.26	1.43	2.87	1.77	1.66	3.23	
3	1.08	1.59	1.53	1.28	2.59	1.40	1.40	3.10	1.58
4	1.37	1.84	1.33	.95	1.59	.90	1.53	2.34	1.44
5	1.47	2.11	1.57	1.01	1.91	1.19	1.44	2.81	1.07
6	1.62	1.84	1.72	1.01	1.34	1.19	1.07	2.06	
7	1.25	2.07	1.28	1.00	1.55	.82	.82	2.83	1.02
8	.66	1.32	1.02	1.93	2.30	1.83	1.50	2.66	1.93
9	1.02	1.70	.95	1.67	2.67	1.74	1.43	1.64	1.43
10	.89	1.42	1.01	1.33	1.30		1.43	3.98	1.51
11	.89	1.28	.89	1.19	1.95	.93	1.51	2.92	
12	1.53	2.09	1.45				1.24	2.50	1.07
13	1.00	1.37	.82				1.75	2.16	
14	1.48	2.73	1.50				2.56	4.69	2.82
15	1.09	2.10	1.36				1.42	3.28	1.59
16	1.06	1.81					1.59	2.71	1.62
17	1.39	1.83	1.29				2.71	4.53	1.62
18	1.29	1.38	1.18					3.36	
19	1.47	1.72	1.28				1.79	2.89	1.97
20	1.28	1.73	1.42				1.07	2.42	1.24
21	.99	1.46	1.19				1.24	2.02	
							2.82	4.46	
							1.17	2.19	1.23
Average	1.20	1.76	1.26	1.28	1.97	1.34	1.59	2.95	1.66 Average

*All figures represent blood plasma tocopherol levels in mg. per 100 cc.

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ELECTROCARDIOGRAPHIC CHANGES IN ACUTE GONOCOCCAL ARTHRITIS AND MYOCARDITIS SIMULATING ACUTE RHEUMATIC POLYARTHRITIS

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It is well known[4,6,12] that from 60 to 80% of patients with acute rheumatic polyarthritis present diagnostic electrocardiographic changes. Although similar alterations of the electrocardiogram may occur in numerous infectious and other febrile diseases, the absence of polyarthritis in these disorders facilitates the differential diagnosis. Reiter's syndrome of urethritis, conjunctivitis and polyarthritis has lately been noted to affect the electrocardiogram[5]; however, the ocular and genital manifestations and its limitation to the male sex serve to exclude acute rheumatic polyarthritis.

In presenting 4 instances of acute gonococcal polyarthritis with electrocardiographic changes, our purpose is to demonstrate a pertinent exception to the axiom that polyarthritis (the usual form in gonorrheal arthritis) plus an abnormal and unstable electrocardiogram is pathognomonic of acute rheumatic fever. We wish also to call attention again to the subject of acute gonococcal myocarditis.

Clinical Abstract.. Case 1. *A 22-year-old woman, with migrating polyarthritis, continuous fever, leukocytosis, rapid sedimentation rate and electrocardiographic changes in the T waves "typical" of acute rheumatic fever, was treated with salicylates without benefit for 49 days. Finally, roentgenography revealed a septic arthritis. Sulfathiazol halted the progressive arthritis and fever in 5 days. One month later the electrocardiogram had become normal. The right knee and left ankle joints were permanently ankylosed. Diagnosis: Septic Arthritis, probably Gonococcal, with Gonococcal Myocarditis.*

S. W. (P. F. No. 887-957), a married negress, age 22, entered the Los Angeles County Hospital on July 19, 1944, stating that she had been quite well until one week before, when the left little finger began to ache and swell. The next day her left foot began to enlarge and hurt; and a day later the right knee became involved. She denied previous arthritis, chorea, trauma, vaginal discharge, and recent pharyngitis.

Physical examination: Temperature 102°, pulse 110, blood pressure 130/70. The tonsils were large, but did not appear infected. The heart was normal. The left little finger, left ankle, and right knee were swollen, red, hot, very tender, and extraordinarily painful on motion. Because of the obesity (200 lbs.) and arthralgia, pelvic examination was omitted.

Laboratory studies: Hb.—12 gm., RBC—4,530,000, WBC—10,650, with 75% PMN, 1% PME, and 24% L. Wet chamber preparations disclosed no sickling of the erythrocytes. Sedimentation rate, 25 mm. (Wintrobe). An electrocardiogram (Fig. 1-A) the day after entry showed low voltage T_1, inverted T_2, T_3 and T_4F and a PR interval of 0.16 second.

Course: Because of the clinical picture plus the typical electrocardiopathy, a diagnosis of acute rheumatic fever was assumed and 160 grains of sodium salicylate were given daily. Nevertheless, fever and arthritis persisted and the right knee became markedly swollen

On August 8 (20th hospital day), a second electrocardiogram (Fig. 1-B) disclosed the PR interval to be 0.20 seconds, with T_3 and T_4F now isoelectric. On the same day, a complement fixation test for gonorrhea was negative; this test plus the abnormal and fluctuating electrocardiograms reinforced the diagnosis of acute rheumatic fever. On August 25 (37th hospital day) fever and arthritis continued; a third electrocardiogram (Fig. 1-C) was similar to the prior tracing; moderate anemia became manifest (Hb—10 gm.; RBC—3,720,000), the leukocyte count was 5,750 and the sedimentation rate was 23 mm. revealed "narrowing of the joint space with irregular erosion of the femoral condyles, most consistent with a septic arthritis." A serial film one month later showed slight increase in the destruction of the knee joint; at this time, the left ankle and foot presented "bony demineralization of the tarsal and metatarsal bones, consistent with septic arthritis." During this period of normal temperature and improvement by treatment with physiotherapy, an electrocardiogram (Fig. 1-D) taken October 16 (89th hospital day) was entirely normal.

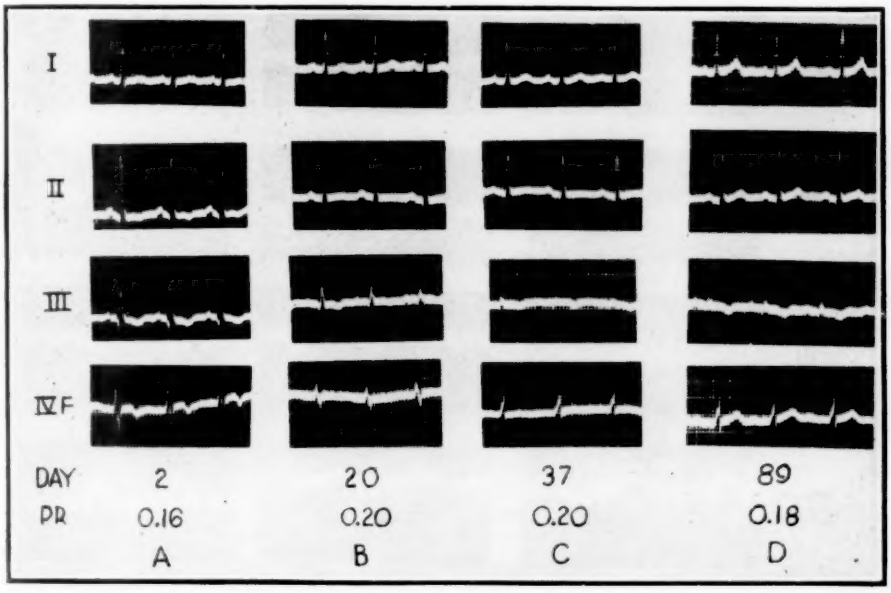

FIG. 1.—Electrocardiograms of Case 1, showing variation in the T waves. A, before treatment. B and C, during salicylate therapy. D, 37 days after sulfathiazol therapy.

Despite no clinical improvement, adequate salicylate therapy was continued for a total of 7 weeks. During this time, the uric acid was 1.1 mg. per 100 cc., a second complement fixation test for gonorrhea was negative, and agglutination tests for undulant fever were negative. On September 9 (52nd hospital day), in the face of a recent spread of the arthritis to the left elbow, salicylates were discontinued and sulfathiazol therapy was instituted; on that day, the leukocytes numbered 10,950, the sedimentation rate was 20 mm., and the hemoglobin had fallen to 8.5 gm. After 5 days of treatment with sulfonamide, the patient became afebrile for the first time in 8 weeks and the pain was greatly relieved. On the 3rd day of this treatment (55th hospital day), roentgenography of the right knee

CASE 2. *A 19-year-old woman with migrating polyarthritis, continuous fever, leukocytosis, rapid sedimentation rate and electrocardiographic changes in the PR interval and T waves "typical" of acute rheumatic fever was treated without benefit for 57 days. At that time a septic joint was disclosed by the x-ray and urethral and cervical cultures revealed gonococci. Penicillin effected a cure in 7 days. One month later the electrocardiogram had become normal. Permanent ankylosis of the right elbow remained. Diagnosis: Gonococcal Arthritis, with Gonococcal Myocarditis.*

O. F. (P. F. No. 817-746), a 19-year-old Mexican housewife, entered the Los Angeles County Hospital on May 29, 1944, complaining of painful swelling of the right elbow and left ankle for 4 days. She denied extramarital

exposure and did not admit sexual contact since her husband's furlough some 4 months prior to entry. There was no history of rheumatic fever or arthritis. Tonsillectomy had been performed 11 years before for frequent sore throats.

Physical Examination: Temperature, 101°, pulse 108, blood pressure 104/80. No cardiac murmurs were heard. Pelvic examination disclosed a normal menstrual period in progress. The right elbow and left ankle were very tender, swollen, red and hot.

hospital day), other joints became painful, the sedimentation rate was 46 mm., and the fever was unabated. In an effort to achieve a therapeutic salicylate level, sodium salicylate was given intravenously according to the method of Coburn. Because a chill occurred after 100 cc. had been administered, the treatment was stopped. Since the patient stated that she had been greatly relieved of the painful joints by the intravenous salicylate, another injection was given the next day and a chill again resulted.

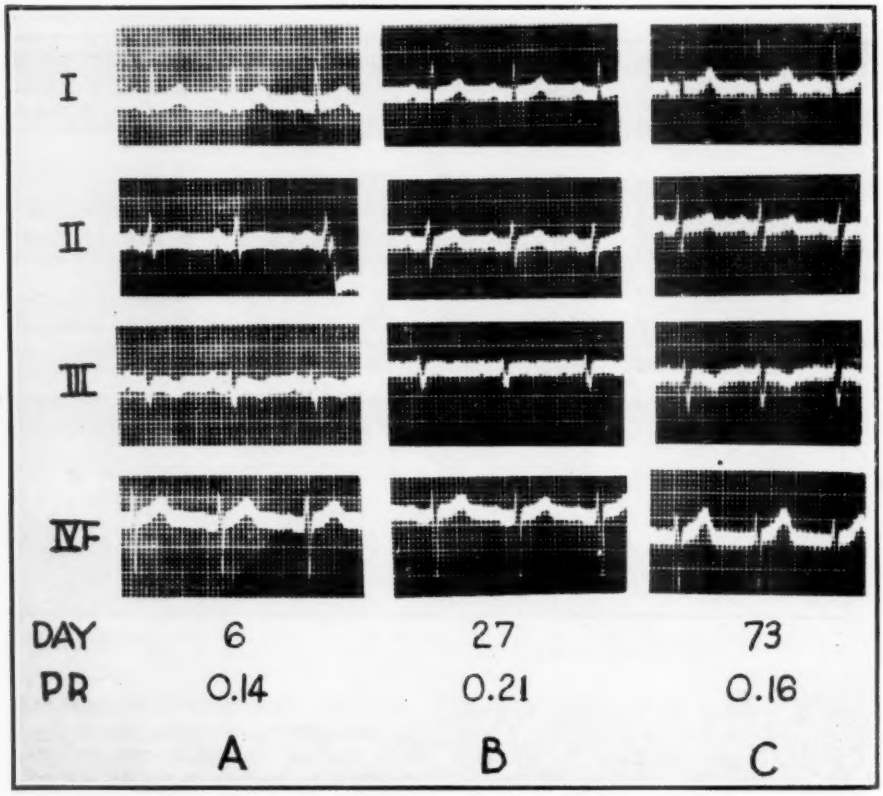

FIG. 2.–Electrocardiograms of Case 2, showing abnormalities of the PR interval and T waves. A and B, during salicylate therapy. C, 16 days after penicillin therapy.

Course. On May 29 (2nd hospital day), cervical and urethral smears showed no gonococci. The sedimentation rate was 34 mm. (Wintrobe). A gonococcal complement fixation test was negative. With all the evidence favoring the diagnosis of acute rheumatic polyarthritis, sodium salicylate was started the next day (12 gm. per diem). On June 2 (6th hospital day), an electrocardiogram showed no abnormality; the PR interval was 0.14 seconds (Fig. 2-A). On June 8 (12th

On June 18 (22nd hospital day), the arthritis had progressed despite salicylate given in adequate oral dosage; the right shoulder was very painful and tender. An electrocardiogram taken on June 23 (27th hospital day) revealed the PR interval to be 0.21 seconds, further buttressing the diagnosis of acute rheumatic fever (Fig. 2-B). The salicylate dosage was increased to 15 gm. per day on June 30 (34th hospital day) without benefit. On July 13 (48th hospital day),

repeated cervical and urethral smears were negative for gonococci. Agglutination tests for the specific fevers were negative. A coccidiodin skin test was negative. The blood uric acid concentration was 1.3 mg. per 100 cc. Four blood cultures were sterile.

On July 14 (49th hospital day), roentgenograms of the right elbow disclosed a destructive arthritis. In a few days, urethral and cervical cultures taken at the time of the second negative smears were reported positive for gonococci. On July 22, confronted with this evidence, the patient confessed an extramarital adventure 2 weeks before the arthritis developed. Penicillin, 20,000 units every 3 hours, was immediately administered. After 1 week she was afebrile and the involved joints, although stiff, were painless.

On August 7, (73rd hospital day), after one week of normal temperature, the electrocardiogram returned to normal with a PR interval of 0.16 seconds (Fig. 2-C). She was discharged the next day able to walk, but with the right elbow ankylosed at 165 degrees. She was examined in the orthopedic clinic at intervals; on September 24 she was still complaining of stiffness of the right elbow, pain in the right knee, and stiffness of the left ankle. An x-ray of the right elbow was reported: "Since July 15, the destruction of the articular cartilage has progressed. The bony demineralization has increased." The left ankle showed "diffuse demineralization and narrowing of the talotibial joint."

CASE 3. *A 21 year old woman developed migrating polyarthritis, continuous low grade fever, leukocytosis and rapid sedimentation rate 15 days before a normal delivery took place. Electrocardiographic changes in the PR interval and T waves were "typical" of acute rheumatic fever. Salicylates were given for one week without benefit and were discontinued when septic arthritis was demonstrated radiologically and a positive complement fixation for gonorrhea was obtained. Sulfadiazine arrested the arthritis and effected a cure in 2 days. The electrocardiogram had not returned to normal 17 days later. A permanently ankylosed ankle joint remained. Diagnosis: Gonococcal Arthritis, with Gonococcal Myocarditis.*

S. M. (P. F. No. 895-817), a Mexican housewife, age 21, entered the obstetrical ward of the Los Angeles County Hospital on September 23, 1944, in the 8th month of her first pregnancy. She stated that she had been well until 3 days before, when she noted swelling of all of her fingers. This was greatly relieved spontaneously, but on the evening before entry the right ankle suddenly became very painful, swollen and hot. There was no history of frequent or recent sore throats, rheumatic fever, or arthritis.

Physical examination: Temperature 99.2°, pulse 100, blood pressure 120/60. The pharynx was normal. No cardiac abnormalities were noted. The uterus was enlarged 22 cm. above the symphysis and fetal heart tones were distinctly heard. The right ankle was swollen, hot, red, tender and was held in plantar flexion. The fingers of the left hand were held in partial flexion and attempted extension was painful.

Laboratory studies: Hb.—11.3 gm., WBC—13,800, with 74% PMN and 26% L. Sedimentation rate: 30 mm. (Wintrobe). Electrocardiogram: T_4F was inverted (Fig. 3-A). On September 25 (2nd hospital day), an x-ray examination of the right ankle disclosed no abnormality.

Course: Spontaneous labor occurred on October 5 (12th hospital day) and she was delivered after a short normal labor of a male child. She had no post-partum complaints except for the painful right ankle. On October 11 (17th hospital day), an electrocardiogram revealed a PR interval of 0.26 seconds (Fig. 3-B). Because of the possibility of rheumatic polyarthritis, suggested by the electrocardiographic changes, she was transferred to a medical ward on the 24th hospital (12th post-partum) day. She was reexamined and again no cardiac abnormalities were noted. Fever was seldom above 99°. The finger joints were now entirely normal, but the right ankle showed no improvement. The leukocytes numbered 16,400 with 74% polymorphs. An electrocardiogram (Fig. 3-C) revealed that the inverted T waves in Leads III and IVF had become upright and the PR interval had returned to normal. A third tracing (Fig. 3-D) taken 5 days later (October 23) showed that T_3 was inverted. An orthocardiogram disclosed a heart of normal size and outline. The blood uric acid concentration was 1.4 mg. per 100 cc. An agglutination test for brucellosis was negative. These normal laboratory and roentgenographic results plus the varying electrocardiograms pointed to a diagnosis of acute rheumatic polyarthritis and the next day sodium salicylate therapy was instituted.

A second x-ray examination of the right ankle (after an interval of 30 days) revealed that the tibio-talar joint was narrowed and hazy, being consistent with a septic arthritis. At the same time a complement fixation test for gonorrhea was reported back as positive. On October 27 (34th hospital day) the salicylate was discontinued and sulfadiazine was given with marked relief of the arthralgia within 48 hours. On October 30 (37th hos-

pital day), the sedimentation rate and leukocyte count were normal. An electrocardiogram, however, continued to show changes (Fig. 3-E); T_3 was upright and T_4F was inverted. On November 8 (45th hospital day), an electrocardiogram (Fig. 3-F) revealed a PR interval of 0.32 seconds. The next day cervical smears were negative for gonococci. An x-ray of the right ankle on November 10 (47th hospital day) showed increased haziness of the tibio-talar joint and further osteoporosis. Clinically, the joint was painless, but ankylosed. On November 13 (51st hospital day) the sedimentation rate was normal, but the electrocardiogram (Fig. 3-G) showed a normal PR interval and lowering of T_1 and T_2. The patient left the hospital against consent and follow-up has been unsuccessful.

stiffness of the neck and fever of 102° were noted. The next day, both thumbs were very tender; this subsided in 36 hours. Four days before entry, both knees became painful and swollen. There was no prior history of rheumatic fever, frequent pharyngitis or arthritis. For several years, she had had nosebleeds a few days before each period.

Physical examination: Temperature 99.4°, pulse 80, blood pressure 110/70. The pharynx was normal. No cardiac abnormalities were noted. Both lower abdominal quadrants were tender. A whitish-yellow vaginal discharge was seen and both adnexal regions were tender. Both knees were markedly tender on their lateral and medial aspects, motion was sharply limited by pain, and the normal surface landmarks were obscured

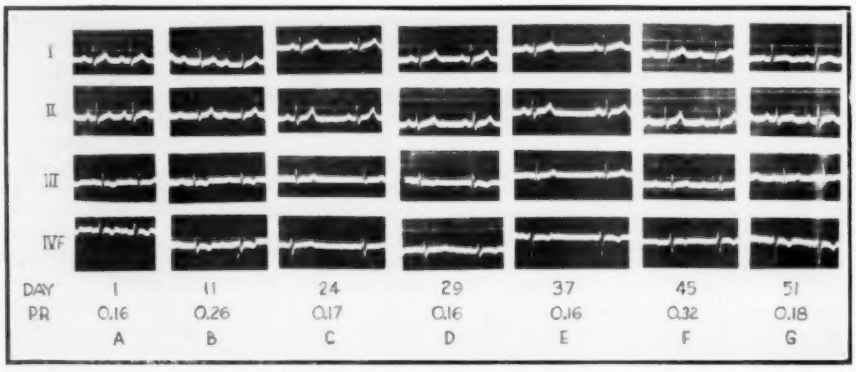

FIG. 3.—Electrocardiograms of Case 3, showing abnormalities of the PR interval and T waves. A, B, C and D, before treatment. E, F and G, after sulfathiazol therapy.

CASE 4. *A 16 year old girl with migrating polyarthritis, continuous fever, leukocytosis, rapid sedimentation rate and vaginal discharge was treated for presumptive gonorrheal arthritis with penicillin and was cured in 3 days. The complement fixation for gonorrhea was positive. Electrocardiograms, however, revealed changes in the T waves "typical" of acute rheumatic fever. One month later the electrocardiogram was still unstable and abnormal. Diagnosis: Gonococcal Arthritis, therapeutically aborted, and Gonococcal Myocarditis.*

C. S. (P.F. No. 936-919), a 16 year old single negress, entered the Los Angeles County Hospital on March 17, 1946, complaining of pain in both knees for 4 days. She had had no abnormal symptoms until a whitish vaginal discharge appeared about one week before entry (and one week after coitus). Shortly after the discharge, burning on urination began. Six days before entry, by fluid in the joints. Both knees were hot, the right more than the left.

Laboratory studies: WBC—11,600. Urethral and cervical smears: no gonococci. Sedimentation rate: 22 mm. (Wintrobe).

Course: On the basis of the admitted coitus and vaginal discharge, acute gonorrhea and acute gonococcal arthritis were diagnosed and 20,000 units of penicillin was given intramuscularly every 3 hours beginning on the day of entry. On March 20 (3rd hospital day), an electrocardiogram (Fig. 4-A) revealed isoelectric T_1, and inverted T waves in the other leads. This might have cast doubt on the diagnosis had not the fever subsided and the arthritis markedly improved. Two days later (5th hospital day) the complement fixation test for gonorrhea was reported positive. Penicillin was discontinued after 5 days; the sedimentation rate was 12 mm. On March 27 (11th hospital day) an electrocardiogram (Fig. 4-B) showed T_1 now

upright and of low voltage. On April 2 (17th hospital day) a roentgenogram of the right knee presented no evidence of septic arthritis. The leukocytes numbered 5,700; the sedimentation rate was 5 mm. She was discharged on the 18th hospital day, the left knee normal, but the right still swollen and tender.

On April 24, 5 weeks after entry, the patient returned to the out-patient department, where the sedimentation rate was 12 mm., and an electrocardiogram (Fig. 4-C) showed QRS_1 now splintered, T_1 and T_2 upright, and T_3F inverted. She felt well.

was ruled out by the development of a septic joint, the failure of an initial attack of arthritis to respond to salicylates in adequate dosage, and, or, the arrest of the septic arthritis and fever by either a sulfonamide or penicillin. In the first case, the septic arthritis was probably gonorrheal in origin, although 2 complement fixation tests were negative. In the other 3 cases, gonococcal arthritis was diagnosed on

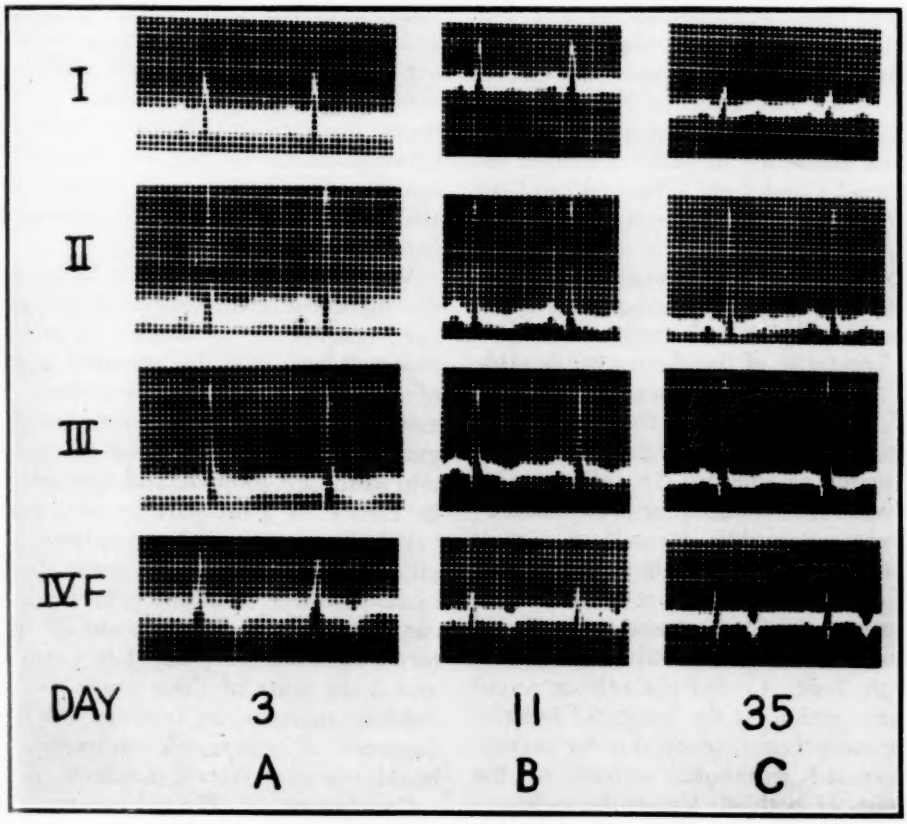

FIG. 4.—Electrocardiograms of Case 4, showing abnormalities of the T waves. All tracings after penicillin therapy.

Discussion. In the preceding 4 cases, the migratory polyarthritis, fever, tachycardia, electrocardiographic alterations and increase in sedimentation rate simulate the criteria proposed by Jones[8] for acute rheumatic polyarthritis. Nevertheless, rheumatic fever

the basis of positive cervical cultures or positive complement fixation tests, the radiologic and clinical evidence of septic arthritis, and the prompt halt of the disease by an antibiotic.

Identical electrocardiographic abnormalities in gonococcal arthritis have

been reported by others without the present nosologic emphasis. Master and Jaffe,[10] in 1934, in a study of electrocardiographic evidence of cardiac involvement in acute diseases, described PR and T wave abnormality in 19 cases of gonorrheal arthritis. Gadrat and Morel[7] in 1935 reported from France electrocardiographic alterations in a man with gonorrheal urethritis and arthritis. Ole Bang,[1] of Copenhagen, in 1940 made the electrocardiographic diagnosis of gonorrheal myocarditis on 6 men, 5 of whom were suffering from recurrent specific arthritis and 1 with acute urethritis and arthritis. He found reference in the European and Scandinavian literature to only 3 similar instances. Candel and Wheelock,[3] in 1945, in a study of 11 patients with diverse illnesses complicated by myocarditis as disclosed by electrocardiographic abnormalities, noted 3 instances of gonococcal arthritis with myocarditis.

The cause of the electrocardiographic alterations in these cases is suggested by Katz,[9] who lists the electrocardiographic changes assignable to acute diseases as due to: 1) Inflammatory myocarditis, transient or permanent; 2) Toxic myocarditis ("result of a toxic action on the myocardium presumably due to some by-product of the infecting organism"); 3) Associated pyrexia, which affects particularly rate and ectopic beat; 4) Sympathetic or vagus nerve action on the heart; 5) Relative coronary insufficiency due to anemia, increased metabolic activity of the heart, or both; 6) Vasomoter collapse; 7) Pulmonary emboli; 8) Coronary emboli.

It is our opinion that the electrocardiographic changes were probably caused by so-called "toxic myocarditis", secondary to the gonorrheal infection. In Cases 1 and 2, the electrocardiogram had become normal within one month after the cure of the gonorrhea. In Case 3, the patient left the hospital on the 17th day against consent while the electrocardiogram was still abnormal. In Case 4, despite a very short total illness of only 6 days of both gonorrhea and arthritis before treatment with penicillin was inaugurated, and the fact that a cure was effected in no more than an additional 3 or 4 days, the electrocardiogram was abnormal and variable on the 11th and 39th day after the onset of treatment.

Isolated myocarditis caused by the gonococcus has never been described anatomically. Saphir,[13] in his painstaking study of myocarditis, was unable to verify any instance of isolated gonococcic myocarditis without an associated endocarditis. In fact, the myocardium is assumed to become infected by the gonococcus via direct extension from the diseased valve.

With these considerations in mind, the myocarditis demonstrated electrocardiographically in Cases 1, 3 and 4 reported here must be assumed to be of the toxic rather than the inflammatory type. In Case 2, the electrocardiographic change was limited to variation in the PR interval, and appears to be caused in great part by increased vagal stimulation. A comparable situation is very common in acute rheumatic carditis.[2] In addition to T wave changes mentioned, significant PR interval increases were noted in Cases 1 and 3. In none of these cases was a diastolic murmur, an essential for the diagnosis of gonococcic endocarditis, heard; nor were emboli manifest.

Conclusions. 1. Electrocardiographic changes and polyarthritis can no longer be accepted as pathognomonic of acute rheumatic fever, because:

2. Identical electrocardiographic alterations and polyarthritis can occur in acute gonococcal arthritis.

3. The electrocardiopathy is apparently caused by toxic gonococcal myocarditis, rather than a true inflammatory lesion.

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AMYLOID HEART DISEASE

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It is the purpose of this communication to bring attention to a small group of patients exhibiting signs of heart disease and intractable heart failure caused by the infiltration of amyloid material into the various structures of the heart. The amyloid disease found in such instances has been designated as primary systemic amyloidosis and differs in several respects from that found in the more common secondary type of amyloidosis associated with chronic suppuration, neoplasm or chronic infections. The major differences between the two styles lie in their different staining reactions to iodine, congo red and methyl violet and their usually distinct organ predilections. The primary type exhibits a marked affinity for smooth and striated musculature, especially that of the myocardium and the tongue, the skin, and blood vessels, whereas the secondary type is characteristically found in the liver, spleen, kidneys, and adrenals. It is the almost universal affinity of the primary type of amyloidosis for cardiac muscle tissue that accounts for the commonly observed cardiac signs and symptoms in this disease. In a recent excellent and complete review of the literature on primary systemic amyloidosis Lindsay[4] reported evidence of cardiac amyloidosis in 39 of 43 autopsied cases. Of a total of 48 reported cases of primary amyloidosis studied by Eisen,[2] 26 (54%) exhibited evidences of clinical congestive heart failure directly related to the infiltration of the heart by amyloid material. Myocardial failure in this disease was usually the result of a widespread interstitial deposition of this foreign amyloid material with consequent stenosis or complete obliteration of the venules and capillaries of the myocardium leading, in many instances, to fibral atrophy and, or, necrosis. Other contributing causes for the myocardial failure were: (a) mechanical interference with the function of the valves caused by the deposition of amyloid in the valvular apparatus, at times giving the clinical picture of organic valvular disease identical with rheumatic heart disease; (b) obliterative infiltration into the walls of the coronary arteries and arterioles and consequent chronic coronary insufficiency; (c) obliterative infiltration into the walls of the pulmonary vessels and alveolar walls with the production of a chronic cor pulmonale; and (d) more rarely, pericardial or endocardial deposits followed by interference of cardiac function.

A report[5] of 3 cases of atypical amyloid disease from Montefiore Hospital in 1935 included 1 case of amyloid heart disease with marked congestive heart failure. Within the last 5 years there have come to autopsy at Montefiore Hospital 2 additional instances of this rare disease, each presenting the picture of intractable congestive heart failure. Clinical and autopsy reports of these cases follow:

Case Reports. Case 1 (E.P., Hist. No. 35812): A 47 year old white male house painter was admitted on April 13, and died on April 22, 1943. He had been in good health until 16 months before admission when he developed a moderately severe upper respiratory tract infection with low grade fever lasting for 1 week. In July 1942, he noted for the first time shortness of breath on climb-

ing stairs and swelling of both legs. These symptoms were thereafter constant, progressive and were soon associated with scrotal edema, classic exertional angina, and a severe cough with scanty expectoration which was occasionally blood streaked. In August 1942 he was admitted to Mount Sinai Hospital because of these symptoms. There he responded favorably to the routine cardiac regime of bed rest, digitalization and mercurialization and was discharged to the clinic on maintenance therapy. At Mt. Sinai Hospital, his heart was found enlarged to the left both on clinical and fluoroscopic examination, with a right axis deviation in the electrocardiogram and no audible murmurs. The cause of the heart failure was uncertain, and suggestions of an occult mitral stenosis or right heart failure due to repeated pulmonary emboli were entertained. In December 1942 he entered Bellevue Hospital with the same complaints, and was discharged unimproved after 2 weeks, despite routine cardiac therapy and a right thoracentesis directed towards the relief of congestive heart failure. Two months later, in February 1943, he re-entered Mt. Sinai Hospital in a state of advanced congestive heart failure which showed practically no response to vigorous therapy. The massive anasarca persisted and the right hydrothorax refilled in spite of numerous thoracenteses. His blood pressure was 126/80 and an electrocardiogram was interpreted as indicative of myocardial damage due to an old anterior wall myocardial infarction. Laboratory data collected at Bellevue and Mt. Sinai hospitals showed a venous pressure ranging between 22 and 25 cm. of water, right axis deviation, prolonged P-R interval, sedimentation rate of 20 mm. in 1 hour, total blood protein of 6.7 (3.7/3.0) and 6 gm. %, negative cephalin flocculation test, normal blood count, cholesterol 200 mg. per 100 cc., a kymographic record showing ample pulsations of

FIG. 1.—Myocardium of the left ventricle. Case 2.—S. L.; Autopsy, 10,576. (x 240). Note the diffuse, wide infiltration of amyloid material between the myofibers. The myofibers are atrophic and degenerated.

the myocardium with no evidence of pericardial fluid, and urine of high concentration showing 1 to 2 plus albumin, a few WBC clumps, an occasional granular cast and an occasional red blood cell. He was transferred to Montefiore Hospital on April 13, 1943, with the diagnosis of chronic interstitial myocarditis, etiology unknown. The past history and family history were negative.

On admission to Montefiore Hospital, the patient was a fairly well developed, tall, 47 year old white male appearing chronically but not acutely ill. The pupils and ocular fundi were completely normal. The tongue was not enlarged nor grossly abnormal. The cervical veins were distended and filled from below. Coarse moist rales were audible above the level of a bilateral hydrothorax extending over both bases of the lungs. The point of maximum cardiac impulse was visible and palpable in the 5th intercostal space near the anterior axillary line. The heart sounds were of good quality, with a distinct gallop rhythm audible at the apex. The rhythm was otherwise regular at 80 beats per minute. P2 was louder than A2. The blood pressure in the right arm was 112/72 mm. of mercury, in the left arm 110/64 mm. There were no thrills nor murmurs. The liver was firm, smooth and its edge extended 4 inches below the costal margin. The spleen and kidneys were not palpable. Edema of the external genitalia was quite marked. The prostate was slightly enlarged symmetrically. There was massive anasarca involving the lower limbs up to the groin and extending on to the sacrum and up to the anterior chest wall. There was no cyanosis nor clubbing of the fingers or toes. Neurological examination was not remarkable.

Laboratory findings: Urine: maximum sp. gr. 1.015 after a concentration test, 1 to 3 plus albumin, and an occasional hyaline and granular cast. The red blood cell count was 4.7 million, hemoglobin 90%, white blood cell count 6800 (67% polymorphonuclear cells, 26 lymphocytes, 5 monocytes, 1 eosinophils, 1 basophils). Serological tests were negative. The fasting blood sugar was 93 mg. per 100 cc. The blood urea nitrogen was 32 mg. per 100 cc. The venous pressure was 20 cm. of water. Circulation time was 29 seconds (ether method), 53 secs. (saccharine). The electrocardiogram showed low voltage, prolonged P-R interval, right axis deviation with right ventricular strain, diminished R4, flat T1, T2, inverted T3, elevated T4. Cardiac fluoroscopy revealed a marked enlargement of the heart transversely with principal enlargement of the left ventricle. Also noted was a bilateral hydrothorax.

The patient's temperature in the hospital was always normal. In spite of vigorous dehydration therapy the patient gained 5 kg. in 9 days. Symptoms were constant and progressive. He was found dead in bed on April 22, 1943, 9 days after admission. The clinical diagnosis was chronic heart failure of unknown etiology, possibly chronic infectious myocarditis.

AUTOPSY. (No. 9510 by Dr. Mae Sherman, 10 hours post-mortem): The *heart* weighed 540 gm. The pericardial surfaces were smooth and glistening and the sac was free of excess fluid. All chambers were markedly dilated and hypertrophied. Friable thrombotic material was adherent to the endocardium of the right atrium and, to a lesser degree, the left atrium. The myocardium was everywhere rather rigid, glistening, pale tannish-yellow, waxy and homogeneous. It measured 16 mm. in thickness in the left ventricle and 5 mm. in the right ventricle. No scars were seen. The muscle gave a positive amyloid stain after the topical application of Lugol's solution. The valves were grossly normal. The coronary arteries were patent throughout with rare small atheromatous plaques. The *aorta* was likewise grossly normal with the exception of a rare and very small atheromatous plaque. The venae cavae were normal. On histologic examination, the myocardium showed a uniform picture of a very diffuse interstitial infiltration by a pale staining material which separated the myofibers. Most of the myofibers were atrophic or degenerative and were surrounded by greatly thickened sarcolemma sheaths which took a bluish stain. Wide bands and nodules of amyloid tissue separated the atrophic myofibers. The coronary vessels showed no histopathological changes.

The *aorta* and main *pulmonary artery* showed considerably and uniformly thickened walls rich in a homogeneous blue staining amyloid material lying between the muscle fibers.

The *lungs* showed chronic passive congestion, basal atelectases and a bilateral hydrothorax. The small and large pulmonary arteries were moderately thickened and exhibited an occasional small intimal plaque. A medium sized artery in the left lower lobe was incompletely occluded by an adherent embolus. The tracheobronchial lymph nodes were anthracotic and succulent. Histologically, the lungs exhibited signs of chronic passive congestion. There was no amyloid in the bronchial lymph nodes.

The *liver* weighed 1640 gm. and showed gross and microscopic evidences of chronic passive congestion and early cirrhosis. The

organ was soft, gave a negative reaction for amyloid with Lugol's solution and there was no amyloid material noted on histological examination.

The *spleen* weighed 190 gm., was extremely firm, tense and purplish-grey. The sectioned surfaces and microscopic examination showed chronic passive congestion and an old healed infarct at the lower pole. The tissue failed to take the Lugol stain for amyloid and no amyloid was found on histological examination.

The right *kidney* weighed 180 gm.; the left 220 gm. They were firm, turgid and exhibited several irregular old cortical scars measuring up to 1 cm. in diameter. The sectioned surfaces and microscopic examination revealed passive congestion but were otherwise normal. The tissue failed to take the Lugol stain for amyloid. The *urinary bladder* and the *prostate* gland were essentially normal.

The *pancreas, adrenals* and *gastro-intestinal tract* were normal except for congestion. Microscopically, the walls of the submucosal arteries in the intestines showed amyloid infiltrations.

The *bone marrow* contained normal bright red marrow. There were no myeloma cells nor any other abnormality.

The neck organs were not removed.

AUTOPSY DIAGNOSIS: Primary amyloidosis of the heart, aorta and pulmonary artery; dilatation and hypertrophy of all chambers of the heart; mural atrial thrombi; chronic passive congestion of the viscera; cardiac cirrhosis of the liver; hydrothorax; ascites; anasarca.

CASE 2 (S.L., Hist.. No. 40742): A 46 year old white female machine operator was admitted to Montefiore Hospital on June 23, 1946, and died on July 18. She had had frequent physical examinations and was always well until 4 weeks ago when she developed a watery, non-bloody diarrhea, occurring about 15 times a day and associated with abdominal cramps. She recovered in 9 days on symptomatic therapy at Beth Israel Hospital. She returned to work and was free from symptoms except for progressive weakness and fatiguability which caused her to cease working several months later. For these latter symptoms she received several injections directed towards correction of an anemia as diagnosed by her local physician. In January 1946 she was treated at Beth-El Hospital for bronchial pneumonia with sulfa drugs and penicillin. During this illness she developed an attack of acute epigastric pain which was diagnosed as biliary colic and confirmed by a cholecystogram. In March 1946 she was readmitted to the Beth-El Hospital for weakness and right upper quadrant pain. She also complained of recent substernal distress, shortness of breath on effort, orthopnea, and paroxysmal cough. Examination at that time revealed a "somewhat enlarged heart with a systolic murmur of the apex", rales at both lung bases, especially the left, and a tender enlarged liver extending 4 cm. below the costal margin. A roentgenogram of the chest showed an "enlarged mitral type heart" and pulmonary congestion. A gastro-intestinal Roentgen-ray series was negative. A moderate hypochromic anemia with normal leukocyte and platelet counts were reported. A 3-plus cephalin flocculation test, a total protein of 5.9 gm. % (3.1/2.8) and normal routine blood chemical study were also reported. She was discharged with a diagnosis of cardiac decompensation and bilateral bronchopneumonia. Two weeks after discharge from Beth-El Hospital she entered the Hospital for Joint Diseases in a state of chronic, moderately advanced congestive heart failure. As this did not respond to digitalis, mercurials, diet and numerous thoracenteses, she was transferred to Montefiore Hospital on June 23, 1946.

On admission to Montefiore Hospital the patient was acutely and chronically ill with obvious respiratory embarrassment. The pupils, ocular fundi, and tongue showed no abnormalities. The neck veins were distended and filled from below. The point of maximum cardiac impulse was on the 6th intercostal space outside the mid clavicular line. The heart sounds were of poor quality. A short blowing systolic murmur, a reduplicated second sound and a short, early diastolic blow were audible at the apex. This diastolic murmur was not audible to all observers. P2 was accentuated and louder than A2. The rhythm was regular at 80 per minute. The blood pressure was 115/70 mm. Hg. A bilateral hydrothorax was more marked on the left. The abdomen was moderately distended by ascitic fluid and a firm, smooth liver which extended to the umbilicus. The spleen was hard, tender and extended 3 fingers below the costal margin. A 2-plus pitting edema of the lower limbs and the sacrum was evident. The neurological examination was not remarkable.

Laboratory findings: Urinalysis: a faint trace of protein, a rare granular cast and a few white blood cells. A complete blood count was normal. The hematocrit was 43%. The blood urea nitrogen was 17.3 mg. per 100 cc. The blood glucose level 83 mg. per 100 cc. The serum albumin was 4.7 gm. %; the serum globulin 1.5 gm. The blood sedimentation rate was 14 mm. in 1 hour. The cephalin flocculation test was negative. The

thymol turbidity was 1 unit. The venous pressure was 17 cm. of water, rising to 18 cm. on liver pressure. The saccharine time 26 seconds. The congo red test showed 59% removal from the blood in one hour. The electrocardiogram showed low T waves and signs of digitalis effect. Roentgenograms of the chest showed a generally enlarged heart, enlarged left atrium and fluid at both lung bases.

The course in the hospital was progressively downhill in spite of diet, bed rest, oxygen, digitalis and mercurials. The patient died suddenly on July 18, 1946. The clinical diagnosis was chronic rheumatic heart disease with mitral stenosis and insufficiency and congestive heart failure.

AUTOPSY (No. 10,576 ,performed by Dr. Alfred Baer 7 hours post-mortem): The neck organs, tongue, larynx, thyroid, and parathyroids were grossly normal. On microscopic examination, amyloid deposits were found in the sarcolemma sheaths of the muscle fibers of the tongue, the walls of the small lingual blood vessels, the basement membrane of the epithelium of the vocal cords of the larynx, and in the interstitial connective tissue of the thyroid gland.

The *heart* weighed 460 gm. The pericardial surfaces were everywhere smooth and glistening with no excess fluid. The myocardium measured 14 mm. in thickness in the left ventricle and 7 mm. in the right ventricle. It was peculiarly firm and was pale tannish brown and waxy. The mural endocardium and the tricuspid, pulmonary and aortic valves were smooth and glistening. The mitral valve was thickened in its distal portion and presented a thin ridge of fine pinkish-grey nodules along the line of closure. The mitral orifice admitted two fingers freely. The chordae tendineae were normal. All chambers of the heart were dilated and their walls slightly thickened. The coronary ostia and arteries were everywhere widely patent and thin walled. The aorta was smooth, elastic and thin walled. On histologic examination, large areas of the myocardium of both ventricles and atriae were replaced by masses of amyloid material. On cross section, the myofibers were frequently surrounded by wide rings of amyloid tissue. The myofibers were often fragmented, granular and focally atrophic. The endocardium of all chambers was extensively infiltrated with amyloid in streaked and mass formations. The intermuscular arteries exhibited amyloid deposits in their walls but the larger subepicardial arteries were normal. The mitral valve contained patches of collagenous fibers lying adjacent to numerous amyloid deposits. There was no evidence of rheumatic valvulitis. The tricuspid and pulmonary valves also showed amyloid deposits as did the aorta within its intimal coat.

The lungs were essentially normal except for the presence of amyloid deposits in the walls of the intra-pulmonary arteries. The main pulmonary artery showed similar deposits in the media and intima with compression atrophy of its muscle fibers.

The *liver* weighed 1800 gm., was firm, waxy, pale brown with a slight pinkish tint (congo red test had been done 1 week previously). Histologically, there was marked amyloid infiltration with compression atrophy of the liver cords.

The *spleen* weighed 650 gm., was very firm, waxy yet friable when cut. Numerous pinhead sized foci with some confluence were noted on the cut surface. Histologically, there were extreme amyloid deposits almost completely replacing the corpuscles and pulp.

The *pancreas* was grossly normal but on histologic examination showed amyloid deposits throughout the connective tissue, in places compressing the acinar tissue. Amyloid was also noted in the blood vessels but the ducts were normal.

The right *adrenal* weighed 8 gm., the left 7 gm. They were fairly firm and had a wide, bright yellow cortex. Histologically extensive amyloid deposits were found in the zona fasciculata with resultant compression atrophy of the cortical cells.

The entire *gastro-intestinal tract* was free from gross abnormality but amyloid deposits were seen throughout the blood vessels and frequently within the mucosal and muscular coats.

The right *kidney* weighed 150 gm.; the left 140 gm. They were soft, flabby and congested. The urinary bladder exhibited a congested mucosa. The Fallopian tubes, ovaries and corpus uteri were absent. The vagina was atrophic. Histologically, the renal parenchyma showed no amyloid material but the arterioles were heavily infiltrated.

The rectus abdominis muscle was pale but otherwise normal on gross inspection. Amyloid was absent on histologic examination.

The *brain* weighed 1400 gm. The *pituitary* weighed 500 mg. Grossly, there were no abnormalities. Amyloid material was found histologically in its vessels.

A strongly positive Lugol test for amyloidosis was found in the liver, spleen, myocardium and endocardium. Weakly positive tests were noted in the kidney, thyroid, adrenal cortex, pulmonary arteries, aorta, pancreas, breast, mesenteric lymph node, esophagus, colon, stomach and small intestine. A

very faintly positive test was found in the tongue and striated skeletal muscle. Congo red stains were done on all tissue sections and the amyloid everywhere failed to take the usual salmon pink color. Instead, it appeared orange and was hard to differentiate from the stain of normal tissue.

Comment. The number of cases of primary systemic amyloidosis that we could find reported is indeed small; the correct antemortem diagnosis has been made in only 8 of the 46 autopsied cases. Yet a careful study by Eisen[2] of the reported cases revealed a fairly definite clinical pattern characterized chiefly by a high incidence of congestive heart failure (54%), macroglossia (42%) asthenia (42%) and weight loss (31%). It is this picture of congestive heart failure with or without macroglossia which sharply differentiates the disease clinically from the secondary type of amyloidosis. Clinical findings and tinctorial characteristics similar to those of primary amyloidosis are found, at times, in the amyloid disease associated with multiple myeloma, but these may be differentiated from the primary type by the classic hyperglobulinemia and plasma cell invasion of bone in multiple myeloma.

The 2 cases described above are reported in order to bring attention to this small group of patients presenting signs of intractable congestive heart failure of unknown etiology. These patients usually show enlarged hearts without evidences of valvular disease, hypertension or coronary sclerosis. Electrocardiographic changes are frequently interpreted as showing myocardial damage in the form of altered T waves, prolonged P-R intervals and low voltage. The most characteristic clinical feature of this type of heart disease is the intractable type of congestive heart failure and a very rapid downhill course in spite of vigorous therapy. As Soma Weiss[6] stated, "without a critical attitude, one is likely to conclude that these patients are suffering from the common diseases of the heart and aorta". The clinical diagnosis is difficult but may be established by the demonstration of amyloid material with bizarre tinctorial reaction in biopsies from the tongue or other skeletal muscle, buccal mucosa or skin. The establishment of a correct clinical diagnosis in such cases could perhaps offer the opportunity for the study of various therapeutic agents such as crude liver extract which has been reported as successful, at times, in the therapy of secondary amyloidosis.[3] Certain strains of inbred mice which develop a spontaneous type of amyloidosis[1] resembling in its distribution the primary amyloidosis of humans may offer an excellent experimental therapeutic approach to those interested.

Summary. Attention is directed to the syndrome of intractable congestive heart failure produced by the deposition of amyloid material in the heart. Two cases of this unusual condition with autopsy are reported. The hope is expressed that a correct antemortem diagnosis may be made in similar cases by a more critical diagnostic approach to those patients with heart failure who present bizarre clinical features which do not fit into the common diseases of the heart.

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THE PNEUMONIA OF MEASLES

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In the past decade the course and prognosis of many of the bacterial diseases has been greatly altered by the application of efficient antibiotic substances. Although no specific agents are available for the treatment of most of the viral infections, the natural history of many of them has been greatly changed because of the effectiveness of chemotherapy in combatting the secondary bacterial complications which often produced a fatal outcome in an otherwise relatively benign disease. It is with one of the bacterial complications of a common viral disease, bronchopneumonia occurring in the course of rubeola, that this paper concerns itself.

Measles is one of the commonest of the acute infectious diseases which affects children, and very few individuals reach adulthood without having had it; Rosenau[5] estimated that about 5 million cases occur annually in the United States. Although uncomplicated rubeola may produce severe illness, it is not dangerous to life unless one of three complications develops; suppurative otitis media, encephalitis, or bronchopneumonia. It is quite difficult to obtain accurate information concerning the incidence of pneumonia in measles because of the inadequacy of reporting of such pulmonary involvement in those who are not hospitalized. This is borne out by the fact that a larger number of cases of bronchopneumonia is noted in patients in the hospital with measles than in individuals treated at home. Furthermore, the criteria used in making the diagnosis of this pneumonia are often questionable, since abnormal physical and roentgenologic findings are quite common in uncomplicated rubeola. Thus, in 3720 cases of measles studied at the Willard Parker Hospital, bronchopneumonia occurred in 22.6%, while in 10,946 patients in New York City[6], many of whom were treated at home, it was present in only 6%. The higher incidence for the hospitalized group is, without doubt, influenced by the fact that many cases of measles are referred to a hospital for care only after they have developed a complication such as pneumonitis.

The purpose of the investigation described in this paper was to study the clinical course of the bronchopneumonia which occurs in rubeola, to establish definite diagnostic criteria for it, to determine, if possible, the bacterial agents involved, and to examine the effects of penicillin treatment.

Methods. All of the patients were admitted to the hospital from August, 1946, to August, 1947. Complete physical examinations and studies of the white blood count and urine were carried out at the time of entry and at frequent intervals thereafter. Cultures of the nose and throat were taken on admission and, in most cases, repeated a number of times during the course of treatment. Blood cultures were made if the temperature was 101F or higher rectally. Blood-heart infusion-proteose peptone-yeast medium was used in all of the bacteriological determinations. Roentgenograms of the chest were made on the day of admission or within 24 hours after coming to the hospital and were repeated periodically in many instances. Oxygen was administered to many of the

individuals in whom a diagnosis of bronchopneumonia was made.

Because of the presence of manifestations of respiratory tract involvement in many cases of measles in which a pulmonary complication is not present, the following criteria were used in making a diagnosis of pneumonia; (1) clinical condition of the patient, (2) degree of respiratory difficulty, (3) physical findings in the chest, (4) roentgenologic abnormalities in the lungs, (5) course of the disease, and (6) laboratory findings, including peripheral white blood count and bacterial flora of the nose, throat and blood. The value of each of these factors in helping to establish the diagnosis of bronchopneumonia is discussed below.

Therapy consisted of penicillin in most of the cases and streptomycin in a few, the choice of agent being decided, in most instances, on the basis of the results of bacteriologic studies of the nose, throat, and blood. Penicillin was given in amounts ranging from 15,000 to 25,000 units intramuscularly every 3 hours and streptomycin in a dose of 0.125 gm. every 3 hours by the same route. Treatment was continued until the temperature had been normal for 5 days, since a shorter period of therapy often led to relapse of the pulmonary disease. Penicillin was exhibited to a number of cases in whom an acute bacterial infection of the lungs was suspected but eventually not proved; these are not included in this report.

Results. SELECTION OF CASES. The patients discussed below were observed at the Haynes Memorial Hospital between August, 1945, and August, 1946, a year during which there were many cases of measles in the communities served by the hospital. Of the 163 patients with rubeola who were admitted during this time, 41 were believed by the authors to have pneumonia.

The differentiation of pneumonia in the presence of such a disease as measles, which by itself often produces inflammation of the respiratory tract (Kohn and Koiransky[4]), is difficult. Even with the most thorough study, there are instances where it is impossible to decide whether true pneumonia is present or whether the patient has only severe, uncomplicated rubeola. The withholding of specific antibacterial therapy might furnish clear cut evidence of infection of the lung in some cases, but such a procedure does not appear to be justified when the suspicion of severe pulmonary involvement due to bacteria is strong, though not completely proved, particularly in young children in whom this disease has a high mortality rate. Because of this difficulty in diagnosis, one or two cases of severe uncomplicated rubeola may have been included and some instances of true pneumonia omitted from this study.

In selecting cases which were thought to have pneumonia, consideration was given to the clinical and laboratory criteria enumerated above. Clear cut Roentgen-ray evidence of pneumonia was present in 21 cases. Three patients had no roentgenographic examinations. The diagnosis of pneumonia in these cases was made for the following reasons: one had cyanosis, leukocytosis of 40 000, many fine crackling rales over both lung fields, and dullness to percussion and bronchial breathing over the right lung base; another showed severe respiratory difficulty, many rales, and a white blood count of 40,000 on admission to the hospital; the third revealed diffuse rales over both sides of the chest, marked respiratory difficulty, and, although the leukocyte count in the peripheral blood was normal, had had a secondary rise in temperature and appeared severely ill at a time when the rash of measles was fading.

In 17 patients who showed Roentgen-ray changes in the lungs consistent with either uncomplicated rubeola or bronchopneumonia, the diagnosis of pneumonia was made on the basis of the presence of respiratory difficulty accompanied by one or more of the following: cyanosis, marked tachypnea, dyspnea, leukocytosis, fever, or abnormal physical findings in the lungs at a time when the mucocutaneous manifestation of measles were subsiding. In 3 cases without increased

white blood counts, cyanosis, or secondary rise in temperature, the severity of the respiratory distress was marked enough to warrant a diagnosis of pneumonia; it is possible, however, that these were merely cases of severe uncomplicated measles.

INCIDENCE OF PNEUMONIA. There were 41 cases of "proved" pneumonia in 163 instances of measles, an incidence of 25.1%. This is, without doubt, not the true rate of occurrence of pneumonitis in rubeola because, as has been pointed out above, hospitalized patients are highly selected and are often admitted only after they have developed a complication of the primary viral infection. Many individuals with mild measles are seen at an infectious disease hospital during an epidemic period, however, because of the necessity of quarantining those who come from boarding schools, colleges, etc., purely as a public health measure. These cases can only counteract, but not cancel, the tendency for patients who are sent to the hospital to be more severely ill than those in the community at large. The incidence of pneumonia in our cases (25%) was substantially the same as that noted at the Willard Parker Hospital (22.6%) some years ago.

SEX DISTRIBUTION. There were 76 males and 87 females with measles; 21 of the males and 23 of the females had pneumonia. This slight difference in the incidence of pulmonary involvement during rubeola in this group is not significant.

AGE INCIDENCE. The ages of all of the patients with uncomplicated measles and those who developed infection of the lungs is shown in Fig. 1. The bulk of the pneumonias occurred in children 5 years of age or under, and there was none in the group 10 or more years old. These findings substantiate the well-known observation that pulmonary complications during rubeola are common in young children but are rare in adolescents and adults. The number of cases of measles over the age of 15 in this series is probably greater than in the population at large, because, although many had mild illnesses, they had to be quarantined in a hospital because they came from schools, orphanages, and other institutions where proper isolation could not be carried out. Thus, the older patients in this group had rubeola that was generally milder than the average in the epidemic, whereas the younger ones represented some of the most severe cases. Rosenau[5] stated that 50% of measles

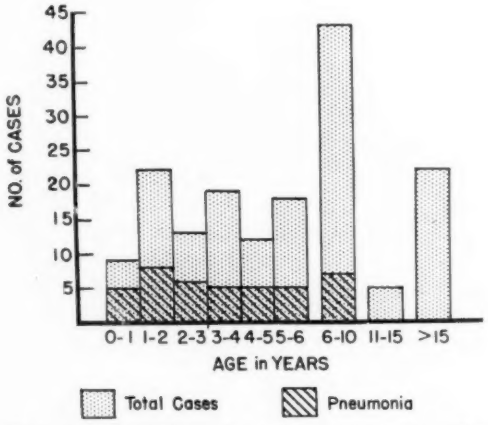

FIG. 1.—Frequency of measles and measles-pneumonia according to age.

occurs under 5, and 97% before 15 years; in the present series, the incidence was 40 and 86% respectively for these two age groups.

SEASONAL INCIDENCE. No cases of rubeola were admitted to the hospital in September, October, or November, 1945. The incidence of the disease rose gradually to a peak in April, remained elevated in May and June, and fell during the summer months. The number of patients who developed pneumonia was highest in March and April at the height of the epidemic (Fig. 2). This may have been due either to increased severity of the measles itself or to the greater prevalence of upper respiratory disease at this season of the year; March and April are the months of peak incidence of scarlet fever in Massachusetts.

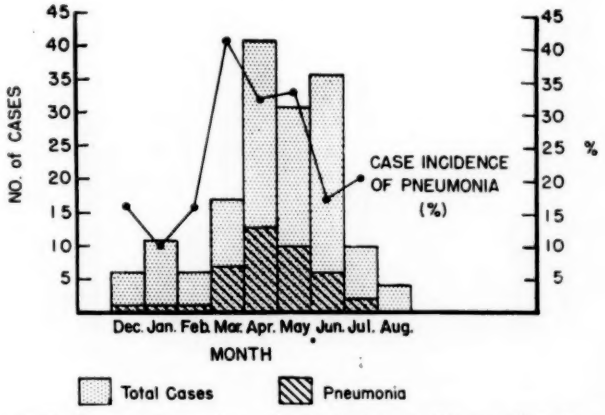

FIG. 2.—Frequency of measles and measles-pneumonia according to season.

PREDISPOSING FACTORS. Underlying disease of a serious nature was common in the patients who developed pneumonia during the course of measles. Two individuals were mongolian idiots with clinically evident congenital heart disease. One case showed a spastic paralysis as the result of a birth injury, 2 had "lipoid" nephrosis, 3 manifested severe anemia, and 1 had eventration of the diaphragm and severe obesity.

A history of frequent severe respiratory tract disease was common. Six patients (14.4%) had had pneumonia from 1 to 3 times prior to developing pulmonary complications during the course of measles. These children, ranged in age from 14 months to 7 years, had first experienced a severe pulmonary infection from birth to the age of 2, and 3 of them had congenital defects; eventration of the diaphragm, spastic paralysis, and mongolism with congenital heart disease.

TIME OF ONSET OF PNEUMONIA. The relationship between the probable time of development of pneumonia to the onset of the rash of measles is shown in Fig. 3. Half of the cases in which the rubeola could be dated accurately showed evidence of pneumonitis early in the eruptive stage. In 7, the pulmonary complication occurred only after the exanthem was fading and in a few, it had already disappeared. Five patients had lung involvement before the eruption appeared, 3 during the prodrome, and 2 in the incubation period. The relationship of the measles to the cases of pneumonia which occurred in the incubation period and the one that came on 15 days after the onset of rash may be somewhat questionable.

PHYSICAL FINDINGS. The physical findings (other than those in the skin) in patients with pneumonia during rube-

ola are presented in Table 1. One child showed no abnormalities in the lungs by physical examination. Rales, which constituted the change found most often in those with complicating disease of the lungs, were present also with great frequency in uncomplicated measles. Dullness to percussion over various parts of the chest was present in 61% of the cases. Although this sign appeared, at first, to be of great help in making the diagnosis of pneumonia, its usefulness was somewhat impaired by the fact that it was discovered frequently when no pulmonary involvement was present; in addition, the location of the dullness was often on the side opposite to the one in which infiltration of the lung parenchyma was demonstrable in the roentgenogram. Bronchovesicular, bronchial and coarse breath sounds were found less constantly and were not reliable indicators of the presence of pneumonia. On the whole, physical examination of the lungs in these patients yielded little information that was useful in making an absolute diagnosis. The presence of a large area of consolidation or a pleural effusion was a much better indication of pneumonitis. Severe dyspnea, flaring of the alae nasi, marked tachypnea, grunting, and retraction of various portions of the chest wall were present in about half the cases and were found only very rarely in uncomplicated measles. Cyanosis, which occurred in 15% of the patients studied, always indicated the presence of pneumonia.

TEMPERATURE. Fever, ranging from 100.8 to 106F (rectally), with a median of 103.2 F, was present in all of the patients at the onset of the pneumonia. In general, the temperature tended to be higher in cases of measles with a pulmonary complication than in those without one, but this finding was of no aid in establishing the diagnosis of pneumonitis in an individual instance. Of considerably greater importance was a secondary rise in temperature after varying degrees of defervescence in the normal course of the rubeola had occurred.

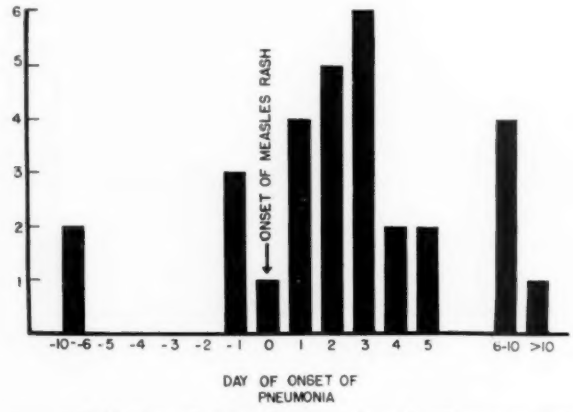

FIG. 3.—Relation between probable time of onset of pneumonia with reference to time of onset of measles.

ROENTGENOGRAPHIC FINDINGS. At least one Roentgen-ray examination of the chest was made in all but 3 of the patients; in Table 2 are summarized the Roentgen-ray findings in the other 38 cases. In almost half the group the only abnormality was hilar and peribronchial infiltration. In 13 instances this was interpreted by the roentgenologist as indicative of bronchopneumonia, while in 4 it was thought to be consistent with acute respiratory infection without pulmonary parenchymal involvement. The diagnosis of pneumonia was most dif-

ficult to establish without question in those who exhibited only this type of roentgenographic change. Kohn and Koiransky[3,4] observed similar alterations in the lungs in 40 to 60% of uncomplicated measles. About 60% of these occurred before or during the height of the eruption; infiltration was often present in clinically mild cases, but was less common in patients less than 1 year of age, and quite unusual in those who had modified rubeola as the result of the administration of immune serum. Six to 10 months later, about 1/3 of the cases revealed pleural thickening; few other residua except occasional localized accentuation of the pulmonary markings were found. The demonstration of pulmonary infiltration by Roentgen-ray examination, therefore, did not make the diagnosis of pneumonia, nor did its absence rule it out. Demonstration of patchy or mottled infiltration, and, or, localized areas of increased density, by Roentgen ray was of much greater help in establishing the likelihood of pneumonia. Abnormalities of this type occurred in 21 of the cases in our series. There was a marked tendency for these to be present on the right side; 3 were in the right upper, 2 in the right middle, and 1 in the right lower lobe; in one instance the exact position of the changes in the right lung was not specified. In only one patient was the area of density found in the left lung: lower lobe. Pleural effusion was demonstrated in only 3 individuals; in 2 it was on the right and in 1 on the left side.

Table 1

Abnormal Physical Findings on 41 Patients with Pneumonia and Measles

Physical Finding	No. Cases	%
Rales	35	85
Altered Breath Sounds	22	54
Dullness to percussion	25	61
Dyspnea	21	51
Cyanosis	6	15
Fluid (Pleural)	3	7
Distention (Abdominal)	2	5

Peripheral White Blood Count. White blood counts made at the time of admission to the hospital and at frequent intervals thereafter were normal or moderately decreased, with a rise in the number of mononuclear cells, in uncomplicated measles. The number of leukocytes present on admission or at the onset of pneumonia, and the maximum count during the course of the pulmonary disease are presented in Table 3. A rise in the neutrophilic granulocytes in the early stages of the pneumonitis was followed by an increase in the mononuclear cells during convalescence. The total peripheral white blood cell count was elevated in 25 and normal or depressed in 16 patients at the time of admission to the hospital or at the onset of infection of the lungs. Rubeola tends to depress the number of leukocytes, whereas pneumonia, particularly that produced by bacteria, elevates it. In a number of the cases reported here, normal counts were replaced by high ones as soon as pulmonary complications developed. Although some of the admission counts listed in Table 3 were not increased, a much better indicator of the true course of events was obtained from a study of the maximum number of white blood cells present during the course of the disease. A single estimation of the white count is not of great significance in establishing a diagnosis of pneumonia; repeated determinations, particularly if a significant elevation occurs and is accompanied by suggestive physical and roentgenographic abnormalities, are of much greater help.

Table 2

Roentgenographic Findings in Lungs of 41 Patients with Measles and Pneumonia

Type of Change	No.	%
1. Hilar and peribronchial infiltration only	17	45
2. Patchy infiltration	6	16
3. Generalized mottled infiltration	4	10
4. Localized densities with or without 1, 2, or 3.	11	29
5. Density in right upper lobe	3	
6. Density in right middle lobe	2	
7. Density in right lower lobe	1	
8. Density in right lung lobe not specified	1	
9. Effusion—right pleural cavity	2	
10. Effusion—left pleural cavity	1	

BACTERIOLOGICAL STUDIES. Cultures of the nose and throat were made on all patients with measles, without regard to the presence of a pulmonary complication. In many of the cases of pneumonia, bacteriologic examination of the upper respiratory tract was performed at frequent intervals during the entire course of the disease. The sputum could not be studied because most of the individuals were young children. Blood cultures were carried out in 21 instances, being repeated several times in some cases. The bacteriological data are summarized in Table 4; the organisms are listed without relation to predominance or the number of times they were present in a single individual. Despite the proved increase in susceptibility to infection with the beta hemolytic *Streptococcus* in measles, this organism was present in only 7 patients. The commonest bacteria recovered were alpha hemolytic streptococci and non-hemolytic *Staphylococcus aureus*. Whether these organisms which are essentially non-pathogenic played a role in the production of the pneumonia in the individuals in whom they were present is difficult to determine. Hemolytic *Staphylococcus aureus* was found in about 25% of the cases. This agent was undoubtedly of great importance since it is known to be a relatively common cause of bronchopneumonia in infants and young children. One of the patients had empyema and another developed bacteremia due to hemolytic *Staphylococcus aureus*. Another organism which was of unquestionable importance was *Hemophilus influenzae*. It was found in 25% of the cases of pneumonitis and produced bacteremia in one individual; this child failed to respond to the administration of penicillin but recovered rapidly after treatment with streptomycin. The other bacteria listed in the table are normal inhabitants of the nose and throat and probably played no role in the production of the pulmonary complications.

TABLE 3

WHITE BLOOD COUNTS IN 41 PATIENTS WITH PNEUMONIA AND MEASLES

Total WBC	No. of Patients On Admission	Maximum
Less than 5,000	4	....
5,000 – 7,900	4	1
8,000 – 10,900	8	6
11,000 – 13,900	5	6
14,000 – 16,900	8	10
17,000 – 20,900	4	5
21,000 – 25,900	3	4
Greater than 26,000	5	10
Median WBC	13,700	16,300

TREATMENT. All of the cases were given penicillin as soon as evidence of pneumonia was detected, without waiting for the establishment of an etiological diagnosis. As a result of the difficulty in determining definitely the presence of infection of the lungs, about 60% more patients were treated than were finally considered to have this complication. The severity of the symptoms, the high fatality rate of untreated pneumonia in rubeola, and the nontoxicity of penicillin seemed to justify the use of the drug in cases in which the suspicion of pulmonary involvement was strong but a definite diagnosis could not be established promptly. The amounts of penicillin used are discussed under **Methods**; data concerning the total dose of the drug as well as the varying periods over which it was given are presented in Table 5. The response to penicillin administration was rapid in most patients, with early defervescence and rapid clearing of the abnor-

TABLE 4

RESULTS OF BACTERIOLOGIC STUDIES OF NOSE AND THROAT IN 41 PATIENTS WITH PNEUMONIA AND MEASLES

Organism	No. of Cases in Which It Was Found Site of Culture		
	Nose	Throat	Blood
Streptococci			
Alpha hemolytic	10	13	
Beta hemolytic	1	7	
Non-hemolytic	4	6	
Staph. aureus			
Hemolytic	10	9	1
Non-hemolytic	16	20	
H. Influenzae	8	11	1
Diphtheroids	6	7	
Micrococcus	1	4	
B. subtilis	1		
P. vulgaris	1		
E. Coli	1	1	
N. Catarrhalis	1	1	

mal physical findings in the lungs. Fifty per cent of the children had a normal temperature after 48 hours of therapy and only 20% were febrile after 72 hours; fever had disappeared in all instances on the 6th day following institution of treatment (Table 6) except in several of those who had complications of the pneumonia. One patient had a secondary rise in temperature accompanied by an increase in severity of the physical changes in the lungs while receiving penicillin; he was found to have developed a pneumonitis due to *H. influenzae*, type B., probably as a result of a change in the bacterial flora of the nose and throat due to the use of penicillin. Treatment with streptomycin produced a rapid, complete recovery. This case has already been described elsewhere in detail (Weinstein[8]) and will not be discussed again here. The patient with *Staphylococcus aureus* pneumonia and empyema was given penicillin both intramuscularly and into the affected pleural cavity (25,000 units every 24 hours). There were no deaths in the entire group of complicated or uncomplicated pneumonias.

TABLE 5

DOSE AND DURATION OF TREATMENT WITH PENICILLIN IN 41 PATIENTS WITH PNEUMONIA AND MEASLES

Days	No. of Cases	Total dose–Units X1000	No. of Cases
4	2	400 – 599	2
5	8	600 – 799	10
6	5	800 – 999	6
7	3	1000 – 1199	7
8	3	1200 – 1399	4
9	6	1400 – 1599	2
10	3	1600 – 1799	2
11 – 15	7	1800 – 1999	1
16 – 20	300	2000 – 2199	3
20	1	2200 – 2399	2
		2400	2

COMPLICATIONS OF PNEUMONIA. Complications of the lung involvement in measles occurred in 5 cases. Two patients had bacteremia, one with *Staph. aureus* and the other with *H. influenzae*; the latter was the same one who developed influenza bacillus pneumonia while being treated with penicillin. Pleural effusion was present in 2 instances; in one there was an empyema due to *Staph. aureus* and in the other the fluid in the chest was sterile. Roentgenographic study of the cardiac silhouette of one child showed findings consistent with an effusion into the pericardial sac; the enlargement of the heart shadow decreased gradually. Since the pericardial fluid was not aspirated, it was impossible to ascertain whether it was sterile or contained bacteria. Parenteral penicillin alone, without instillation of the drug into the pericardial sac, produced a complete cure. The *Hemophilus influenzae* pneumonia which devoloped as a complication of a lung infection due to some other agent has already been mentioned.

Discussion. The virus of measles produces a variable degree of respiratory involvement in most cases. Roentgen-ray studies indicate a high incidence of pulmonary infiltration even in mild instances of rubeola. Non-productive cough is one of the most constant clinical features of the disease. Pathologic examination of the lungs of those in whom death has occurred during the course of a non-bacterial pneumonitis complicating measles has revealed monuclear exudate, giant cells (Algana and Warthin-Finkeldey types), nuclear inclusions in the tracheal, bronchial and alveolar epithelium, and ulceration of the surface of various parts of the respiratory tract due to necrosis of the epithelial cells.

TABLE 6

EFFECT OF PENICILLIN TREATMENT ON TEMPERATURE IN 41 PATIENTS WITH PNEUMONIA AND MEASLES

Temperature	Days of Treatment and No. of Cases						
	0	1	2	3	4	5	6
106 or over	2						
105 – 105.8	5	2	1				1
104 – 104.8	9	2	1	1	1	1	
103 – 103.8	9	9	6	1	1	1	
102 – 102.8	10	6	3	4	2		
101 – 101.8	5	9	8	8	4	3	
100 – 100.8	1	9	7	9	7	4	3
100		4	15	23	26	32	36

Bacteria are of unquestionable importance in the production of pneumonia in many cases of measles as is

shown by the development of empyema and/or bacteremia due to *Staph. aureus, Strep. pyogenes,* or *H. influenzae.* The increased susceptibility of individuals ill with rubeola to infection with the beta-hemolytic Streptococcus is too well known to require further comment; in some epidemics, for example the one that occurred in Army camps in 1918, there may be a high incidence of streptococcal pneumonia with empyema. The role of other less pathogenic organisms in this type of pneumonitis is not so well understood but *Strep. viridans* and non-hemolytic Staphylococci have been found in the lungs in fatal cases. The part played by bacteria in the production of pneumonia in a particular case of rubeola is difficult to evaluate, even when highly pathogenic organisms are recovered from the nose and throat; they may be present as a result of otitis media, sinusitis, or pharyngitis or may only be normal inhabitants in these sites, as is the situation in healthy carriers. Exact bacteriological correlation is impossible in most instances because of the inability to obtain sputum in young children; tracheal cultures and puncture of the lung are not practical enough for wide application. The pneumonitis which occurs in measles may be due to the virus itself or to secondary infection with bacteria. The relative role of each of these agents varies from one case to another and is difficult to evaluate in any particular instance unless certain findings are present. A high white blood count with relative increase in the percentage of polymorphonuclear leukocytes, favorable response to penicillin treatment, bacteremia, or the development of a complication such as empyema, pericarditis or bronchiectasis are highly suggestive of bacterial invasion rather than pure viral infection.

Since a varying degree of respiratory tract involvement is present with great frequency in uncomplicated measles, the diagnosis of pneumonia is difficult to establish definitely in some cases. The application of the following criteria is helpful in reaching a decision concerning the presence or absence of a pulmonary complication: (1) the general clinical condition of the patient, (2) the degree of respiratory difficulty, (3) the chest signs, (4) roentgenograms of the chest, (5) clinical course of the disease, (6) peripheral white blood count, and (7) bacteriologic studies of the nose, throat, sputum, and blood.

The clinical condition of the patient and the degree of respiratory difficulty are of much greater value than the physical findings over the lungs in making a diagnosis of pneumonia in rubeola. Roentgenograms are diagnostic in a little over half of the cases. In instances where physical and Roentgen-ray examination of the chest are of little help, the clinical course of the disease, the peripheral white blood count and bacteriologic studies are often the deciding factors. A secondary rise in fever late in the eruptive stage or failure of the fever to decrease with subsidence of the rash, particularly when accompanied by significant physical and roentgenographic findings, makes more certain the possibility of pneumonia. Increase in severity of the cough, spread of the physical abnormalities in the lungs, or a peripheral white blood count greater than 10,000 with a shift to the left are highly suggestive. The isolation of pathogenic bacteria in large numbers from the nose and throat may also be of aid. When this is the case, however, there is usually other very good evidence of a pulmonary complication; a positive blood culture has much greater significance.

The favorable results obtained in the treatment of the cases of pneumonia reported here with penicillin are very striking. There were no deaths in spite of the severity of the disease in some of the patients. There were only 2 individuals who failed to respond to the usual doses of penicillin: one case of

empyema which was present before any therapy was given and another of *H. influenzae* pneumonia and bacteremia which occurred during therapy; both of these recovered with the exhibition of other forms of treatment. These results are in marked contrast to those obtained at the Willard Parker Hospital[1] and the Kingston Avenue Hospital[2] where the mortality rates were 63 and 14.9% respectively in untreated cases of pneumonia complication measles. In the cases of bronchopneumonia and rubeola treated by Swyer,[7] the incidence of fatalities was 10.3% in those given sulfapyridine and 21% in those not treated. Gibel and Litvak[2] administered sulfathiazole to 53 individuals with the same disease and reduced the deaths to 1.8%.

It is possible that the excellent therapeutic effects obtained in the group described in this paper are due to the inclusion of cases with either no true pulmonary complication or with only very mild pneumonitis. A serious effort was made, however, to apply strictly the criteria discussed above but, even with this, a number of patients were treated who, in retrospect, were finally not thought to have the disease; these are not included in the present report. Comparison of the incidence of pneumonia in our series, (25.1%), with those of the investigators cited above (22.6% at the Willard Parker Hospital, 7% at the Kingston Avenue Hospital and 13.3% in Swyer's group) is impossible because the diagnostic criteria used by them are not described.

Despite a possible variation in the criteria used for diagnosis, the results of penicillin treatment were so favorable as to leave little doubt that it is the agent of choice in the treatment of patients with measles who develop pneumonia. Since the response to this antibiotic agent was so striking in the vast majority of cases, 2 assumptions can be made; (1) a very large number of the pneumonias that occur in rubeola are either due directly to bacterial infection or are the result of secondary invasion of the lungs by these organisms; (2) most instances of this type of pulmonary involvement are due to Gram-positive bacteria since these are the ones most susceptible to penicillin. The bacteriologic studies of the nose and throat supported this conclusion.

The diagnosis of the pneumonia that complicates measles is difficult to establish with certainty but every effort should be made to evaluate each patient as accurately as possible by the application of the criteria enumerated above. In instances where a decision cannot be reached, the patient is seriously ill, and the suspicion of a pulmonary complication is strong, penicillin should not be withheld, because delay may result in a fatality. On the other hand, the antibiotic should not be used indiscriminately since its use may cause sensitization unnecessarily or, as Weinstein[8] has pointed out, may lead to new pulmonary infections produced by agents insensitive to its action; this is particularly true in individuals suffering from an underlying acute or chronic pulmonary disease. The case of *H. influenzae* pneumonitis and bacteremia described above is an example of this phenomenon.

Summary and Conclusions. 1. Pneumonia was found in 25% of 163 cases of measles.

2. Pulmonary complications appeared to be more common in children under the age of 5 than in older individuals.

3. Of the patients studied 50% developed the bronchopneumonia in the early stages of the eruptive phase of rubeola.

4. The definitive diagnosis of serious pulmonary involvement in measles was difficult because of the frequency with which the uncomplicated exanthem is accompanied by physical and roentgenographic abnormalities in the lungs.

5. The application of certain clinical and laboratory criteria was of help in establishing the diagnosis of pneumonia.

6. Most of the serious bronchopneumonias which occurred in the course of rubeola appeared to be due to Gram-positive bacteria.

7. Penicillin appears to be the agent of choice in the treatment of pneumonia in measles; of a group of 40 patients treated with this drug there was not a single fatality.

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HOME ACCIDENTS AS A COMMUNITY HEALTH PROBLEM

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WHEN physicians long ago extended their interests from the care of the sick and injured to include prevention as a coordinate activity, the emphasis accorded that concern developed a peculiar imbalance. Prevention evolved as a matter almost wholly related to disease, at first concerned with the communicable diseases, but solidly and progressively advancing to include most of the affairs of the sick. The injured have received much less attention, perhaps because the approach to prevention is less well defined, and partly because accidents and injuries are too commonly regarded as unavoidable, as matters of chance to be endured and patched up but scarcely to be prevented. That attitude is not far removed from the beliefs about disease that were held some centuries ago.

The view gradually gains acceptance that traumatic injuries are preventable, and to a greater extent than many of the diseases having active programs of control. Neither disease nor injury is to be understood as an evil, a misfortune, bad luck or a mistake of nature, but as the result of a broad biologic law, an expression of life. The answers to why and how accidents have come to be what they are, to behave as they do and to occur in the places they are found, are to be sought in the mass pathology of traumatic injuries as evidenced by modern communities, in other words in the epidemiology of accidents.[21c]

As so often happens with public health problems, the first attention to accidents as a community responsibility centered on the unusual and dramatic misfortunes that affect appreciable groups of people. The catastrophes associated with hurricanes, floods and fire led to establishment of a national organization for disaster relief by the American Red Cross,[41] the first operation having been in the Michigan forest fires of 1881. Again so typically, the original purpose was not prevention but

to afford relief to the victims of these cataclysms. Poisonings of children by lye[24] and the traumatic injuries once so much a part of celebrations of American Independence Day[2a,2c] were natural and early interests of medical organizations. Here the concept of prevention was sharply and forcefully introduced.

As motor cars progressively supplanted horses, a new factor was introduced into the causation of accidents and fast came to rank ahead of most others. The Federal Government took an early interest in the matter through the National Conference on Street and Highway Safety, called by Secretary of Commerce Hoover in 1924. The National Safety Council[7] joined in this through their newly organized Public Safety section. When the frequency of these events reached an all time high in 1936, along with accidents in general, medical organizations joined with others already active to study the situation and to make recommendations. A special committee of the American Medical Association reported in 1939.[2b] The upward surge in numbers of traffic deaths in 1946, following the removal of wartime restrictions on motor travel, caused a renewal of Government interest and the appointment of the President's Highway Safety Conference.[34] What has been accomplished by government and voluntary agencies has led to improvement, but is far from a satisfactory solution of the problem.[29a]

This worth while concern with spectacular and pressing events had by no means left the ordinary affairs unattended, *i.e.*, that large bulk of accidents in the home and at work which constitute the principal cost in accidental deaths and disability. Over the years, American industry[4a,4b,30b] has given so much emphasis to accident prevention[23] as to engender a common opinion that the field is largely limited to occupational injuries. This comes about, not because industry contributes the most accidents, but because it has done the most about them.[27]

The appreciation that official public health agencies had a responsibility in accident prevention was a matter of slower evolution. Leadership came first from welfare, police and other local governmental authority, from industry, from voluntary agencies such as the National Safety Council[30c] and the Metropolitan Life Insurance Company,[19] and through various agencies of the national government.[29b] The pioneer public health interest in accidents was originally not far from a one man crusade by Earle Brown[13] in Kansas and later in Nassau County, New York. The interest spread. When the Association for State and Territorial Health Authorities met[36] in 1941, the principal attention was to motor accidents but much time was devoted to home and other forms of accidental injury that occur in the normal course of life under peace-time conditions. The American Public Health Association[3b] has since 1942 stressed home accidents as a public health problem. Increasing numbers of state and city health departments have organized divisions for accident control, of which those now existing in Kansas,[26] in New York state[38] and as proposed for Massachusetts[16] are good examples. A stocktaking of accomplishment and an evaluation of the current situation can be undertaken to advantage. Accordingly, the accidents of civilian populations are here first defined and examined as a community health problem. Home accidents are then presented as the particular concern of medicine and public health.

Accidents Defined. An accident is universally understood to be a chance event, developing without foresight or expectation, and resulting in injury, or loss. This broad interpretation must be brought within narrower limits when accidents are considered as a health problem of groups of people, for evi-

dently the episode may relate to a person or a thing, to an injury or a material loss, and may be serious or slight. The first restriction is thus to accidents of sudden traumatic origin that result in physical injury to the person.

A number of practical considerations enter into the limitations to be placed on the seriousness of the effect that follows. To confine attention to fatal accidents is to neglect the losses of time and efficiency[17] that come from temporary disability and permanent physical defect. Economically and socially, these are often more important than death. To account for all of the minor disabilities resulting from inconsequential mishaps is to dissipate effort needlessly, and to divert emphasis from really important matters. Disabling accidents are the significant consideration.

The American National Health Survey of 1936[32] interpreted a disabling accident as any sudden bodily injury that resulted either in disability lasting one week or more, in admission to hospital irrespective of time, or in death. The National Safety Council [30c] considers an accident to be disabling if the effect is prolonged past the day of occurrence. Where concurrent recording is followed the period of two or more days disability is a practical and workable criterion. For survey purposes, where information is collected retrospectively about events within the preceding year, accuracy requires that the period of disability be sufficiently great to be well remembered, hence one week. Each period is individually suited to the purposes to which it is put, but a clear definition is necessary if logical comparisons are to be made.

The stated interpretation of a disabling accident is evidently far broader and more inclusive than the commonly held opinion which limits accidents of community concern to catastrophes, where 5 or more deaths follow a single misadventure, or to what are statistically classed as cataclysms. A great variety of wholly ordinary affairs of life comes into consideration, and it remains so to arrange them in an orderly classification as to permit satisfactory comparison of the experiences of one community with those of another.

A Classification of Accidents. The classical procedure for the separation of diseases as they affect individuals is according to the parts of the body primarily affected. The same principle is applied with equal ease to the mass diseases of communities, where disease in such geographical units of population as rural, urban, farm or suburban, forms the counterpart of involvement of the respiratory tract, the circulatory system or other of the great anatomic divisions of the body in the individual person. Specifically, so far as accidents are concerned, the accepted procedure is first to distinguish those mishaps which occur in people's homes from those associated with places of work. All others are classed reasonably enough as public accidents, since they occur in public places, but with one notable exception. Motor accidents in public places are accorded separate recognition because of the numbers involved and the peculiar features associated with the problem. Four great groups of accidents are thus recognized, those that occur in homes, at work, in public places and in association with motor cars.

In order to follow a classification of accidents according to place of occurrence, several arbitrary restrictions must be made. Since home accidents include by definition all mishaps occurring in the home or on the home premises, a limited number of motor vehicle accidents are included, in 1947 about 100. Public accidents include all mishaps in public places, except those associated with motor vehicles. Motor vehicle accidents will be taken to include all that occur in public places, whether asso-

ciated with occupation or not, for the reason that a large proportion of motor cars are used for both business and pleasure and much inexactness results from an attempt to determine in which capacity the car was engaged at the time of the accident. The occupation of a physician is evidently the practice of medicine and scarcely that of operating a car for profit. The motor accident that he has may or may not be in the course of his professional duties. The decision as to occupational use is thus open to a variety of interpretations. Truck operators are evidently in a special category, but the accidents they have occur in public places and are associated with motor cars, in 1947 accounting for about 2,500 fatal accidents. They are included with other motor vehicle accidents. The class of occupational accidents as here considered is best stated as occupational, civilian and non-motor vehicle.

Accidents as a Current Health Problem of the United States. Because the effectiveness of prevention depends on specifically directed action, and because that specific action in turn depends on detailed knowledge of the causes of disease or injury, the first objective in the study of a community health problem is to determine its size and its general nature. Recently released vital statistics show that in 1947 some 99,579 deaths in the United States[2e] were the result of accidents, a mortality rate of essentially 69.4 per 100,000 population. The data correspond closely with preliminary estimates of 100,000 deaths by the National Safety Council.[30c]

Civilian accidental deaths when divided into the four categories stated, show 34,500 home accidents (35.0%), 31,700 motor vehicle accidents (32.1%), 18,000 accidents occurring in public places (18.2%) and 14,500 (14.7%) occupational non-motor vehicle accidents. These proportions are for the United States as a whole. Local conditions and environmental differences lead to appreciable variation, as indicated by the 1947 results for the state of Tennessee,[40] where the distribution was home accidents 34.3%, motor vehicle 36.3%, public 21.3%, occupational 6.2% and other and unknown 2.0%. Motor vehicle accidents exceeded home accidents, the example being selected not because of that circumstance, but principally because the records there are particularly good.

An evaluation of any community or mass disease on the basis of deaths is not the method of choice, for judgment is more satisfactory and informative when the number of events that occur is also available. With accidents and with many of the more important diseases, cases are not officially or uniformly collected and made a matter of record. Deaths are and, as a consequence, the principal interpretation is necessarily made of those data.

The temporary disability associated with a disease condition may be a far more important health consideration than the deaths that occur, as with the common cold. Under other circumstances the proportion of affected persons left with a permanent defect may outweigh the losses from deaths, when the two are viewed on the basis of expected productivity and usefulness during life expectancy.[17] Lacking general and complete information by which to judge the losses from defect and disability, an approximation can be had by local surveys of fatal and non-fatal events. If the surveys are sufficiently extensive and the sample is tested for reliability in respect to the whole, a factor can be derived which will give a reliable index on the basis of known deaths, of the numbers of non-fatal accidents leading to temporary disability, and similarly the number associated with permanent impairment of function.

Thus the National Safety Council[30c] has published estimates for 1947 based

on data from the National Office of Vital Statistics, state industrial commissions, state traffic authorities, state departments of health, insurance companies, industrial establishments and other sources. Of a total of 10,600,000 accidents resulting in death or a disability lasting longer than the day on which the accident occurred, 380,000 caused permanent impairment of function, to include partial and total disability of all grades. Translated into terms of morbidity rates, and using current estimates of population, the approximation of 74 disabling accidents each year per 1,000 population is obtained. Sub-divided to give results of disabling accidents in terms of death, defect and disability, the rates per 1,000 inhabitants of the United States, to include both civilian and military populations, are in 1947 respectively 0.7, 2.5 and 71. The more informative expression in terms of man-days lost, as a means of presenting losses from non-fatal accidents, is not possible for accidents as a whole, nor for the specific categories of home, public and motor vehicle accidents, although good information is to be had for various industries.

The direct cost of accidents as judged by death, disability and defect is scarcely representative of the total effect on health, for the financial cost of accidents exerts an important indirect effect through economic pressure, especially when the wage earner or other responsible member of the family is concerned. Estimates of this cost developed by the National Safety Council, despite all the inherent inaccuracies that must attend such appraisals, nevertheless give the almost incredible total of $7,100,000,000 as the cost of accidents in 1947. This includes wage losses, medical expenses, overhead cost of insurance, property damage, fire loss and indirect costs involved in such things as interference with production and time lost by workers other than the injured.

The favorable record of 1947 in respect to deaths from accidents was attained despite what appears from the simple total of well known events to have been a year with a somewhat greater than usual proportion[39f] of losses from catastrophes. The data are not yet available. These irregular and opportunist occurrences that involve appreciable numbers of people introduce frequency variations comparable to the fluctuations seen in communicable disease and brought about by epidemics. Whether occurring in mass disease or in mass injury, they introduce factors that influence the interpretation of behavior.

The difficulties of the epidemiologist in defining an epidemic of communicable disease are avoided by the statistician through arbitrary decision that a single accident resulting in 5 or more deaths constitutes a catastrophe. The circumstances are variously related to air, water, rail, and motor transportation, to fire, marine, flood and storm, to poisonings, to the accidents of mines and quarries and to events such as earthquakes and explosions. The number of catastrophic deaths[39e] for 1946 has been estimated as 1,074 resulting from 103 accidents, while the 10 year average for 1937 to 1946, was 1,299. The more restricted class of cataclysms, representing deaths from tornado, flood, hurricane and similar disasters, is included in these data. For 1946 such deaths[29b] numbered 148. Three conclusions follow.

The first inference is that these catastrophic, unusual and often terrifying events are but a small factor in determining the totals of those who die from accidents in the United States, since they account for only about 1%. Secondly, the over-all record of 1947, one of the most favorable in all of the years that records have been kept, came despite what appears to be more than the usual contribution by these unusual events. Finally, the deaths and disabil-

ities that result from traumatic accidents are a relatively fixed and regularly recurring health hazard of more or less constant presence. They correspond in their behavior to the endemic pattern of infection that characterizes so many communicable diseases.

ACCIDENTS AS A WORLD HEALTH PROBLEM. Differences in classifying deaths due to accident, the varying inclusiveness of reporting, the irregular practices about excluding military accidents and a variety of other factors, make a sound comparison of accident rates between countries impossible. The data of Table 1 are selected from information submitted by 38 countries with the purpose of showing the universal existence of the problem, the range of reported rates and the consistent importance of accidents as a public health problem. Judged by this experience, the United States stands in the upper quartile of countries reporting, with a rate that is exceeded by few countries.

TABLE 1.—DEATHS FROM ACCIDENTS PER 100,000 POPULATION, UNITED STATES AND SELECTED FOREIGN COUNTRIES

Country	Year	Rate
Venezuela	1944	27.5
Portugal	1946	36.1
Belgium	1946	41.1
Sweden	1944	48.1
Switzerland	1944	55.1
Finland	1944	60.8
United States	1946	70.1
Iceland	1940	77.6
Austria	1946	85.3
Egypt	1943	115.8

Source: Statistical Office, United Nations, official reports by countries.

ACCIDENTS AND DISEASE AS CAUSES OF DEATH. Existing United States rates for civilian deaths from accident and violence remain numerically at almost the identical level of 1900, 88 per 100,000 population in 1900 and 88 in 1946. The relative position among public health problems is at a higher level[39g] since these combined conditions have advanced as a cause of death from sixth place in 1900 to third in 1946. In 1900 tuberculosis and two other infectious diseases, together with diseases of the heart and nephritis, all caused more deaths than accidents and violence; now in 1946 only cancer and heart disease do so. If accidents are considered alone, 3 diseases are responsible for more deaths.

The military situation is equally informative. Over a long history, disease has been the principal cause of death in armies, even exceeding battle casualties in time of war. Non-battle injuries, the category largely representative of accidental deaths, were a relatively minor consideration. In the European phase of the 1917-1918 and the 1942-1945 wars, the death rates for injuries among American troops were almost identical for the two wars, about 2.3 per 1,000 per annum,[21b] but the relation of injury to disease was completely reversed. Disease caused 9 times more deaths than injury in World War I; in World War II injury exceeded disease in essentially the same proportion.[21a] This trend was already evident in peace time, for the 1939 death rates for the American Army[15] showed 53% of deaths due to injuries and 43% the result of disease.

TRENDS IN ACCIDENTAL DEATHS. A well judged prognosis is as useful in problems of mass disease as with illness

of the individual patient. The outlook is none too happy for any immediate improvement in the accident situation. The gains in death rates since 1900 are not great. For the country as a whole the usual range was from 80 to 90 deaths per 1,000 population in 1900. In recent years it has varied between 70 and 80, and currently is on the borderline of 70. A material improvement got underway shortly before 1920, only to be balanced by the newly introduced factor of the motor car. The increasing numbers of deaths from motor accidents have just about neutralized the gains since made against previously existing conditions. About that same time another factor came into increasing prominence, the aging of the American population. With more people living past 65 years, more were added to the group which consistently has the highest accident rates. This again discounted a potential improvement, and gave further example of how a changing environment, a shift in ecologic equilibrium, acts on health and disease in man.

The ten states and the District of Columbia that comprised the United States Registration Area of 1900 (Fig. 1) perhaps serve best in comparing conditions in 1900 with those of 1946, since many variables are eliminated by choice of a uniform area rather than the progressively enlarged territory included within the registration area as time went on. So judged, an improvement has taken place, particularly in recent years and largely through the lesser effect of motor accidents during the war years. It remains to be seen if these gains can be held. To do so will require improved methods and a greater energy in control measures, for the important factor of the motor car assumes increasing weight.

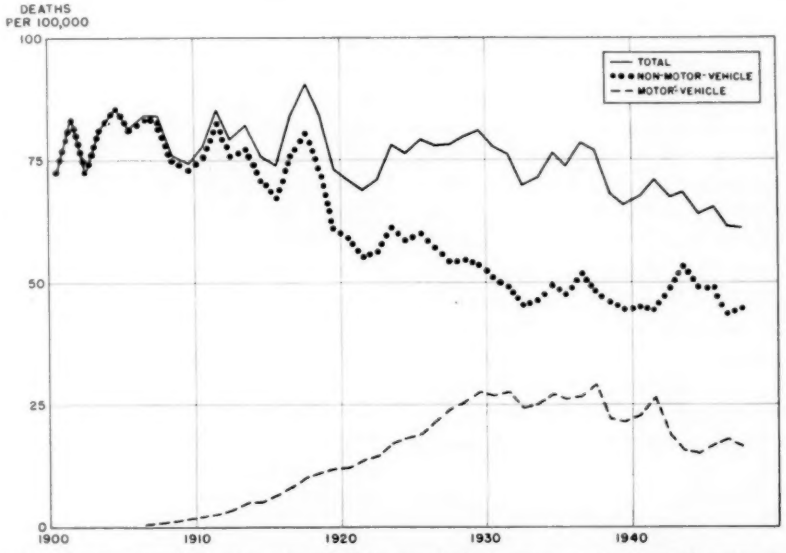

FIG. 1.—Accidents, mortality rates per 100,000 population, states of the United States Registration Area of 1900, 1900-1947[29b,30c].

PATTERNS IN HOME ACCIDENTS. The accidental injuries that occur in the home are believed to be the particular province of public health and preventive medicine. This implies no conflict with accepted principle, that the maintenance of community health is a community function in which most agencies

of government take part and where a variety of skills is required whatever the problem. The physician regularly has a part, although his activities are reasonably greater in some fields than others.

The main responsibility for the accidents of industry is clearly with the safety engineer, while motor accidents and the diverse mishaps in public places are the special concern of the police and other law enforcement authorities. This may account for the general lack of interest in accident prevention by public health agencies and by private practitioners through preventive medicine. The more likely reason is a failure to dissect the problem; to appreciate that accidents are the fourth cause of death in the United States; and to recognize that wherever they occur and whatever their nature there are many medical considerations. More important still is the inadequate understanding that accidents in the home are numerically the largest class of all; that progress in prevention has been less than with any other accidental injury; and that the only promise for a successful approach seems to be through the facilities and the technics possessed by health departments[3a] and by practitioners of medicine.[8]

Home Accidents as a Health Problem. The case for home accidents as a community health problem is readily made. Of all deaths from accidents among the civilian population of the United States in 1947, 35% were due to injuries sustained in the home, this being the largest among the four principal classes just defined. Of nonfatal accidental injuries, essentially a half were of that origin, 5,200,000 of a total of 10,520,000. Some 140,000 persons were left with a permanent physical defect as the result of a home accident. Thus for every death 150 others were temporarily disabled, more than for any other class of accident, and 4 suffered a permanent impairment that varied from minor disability to complete crippling, these and other data being estimates of the National Safety Council. The death rate for home accidents in 1946 was 24 per 100,000 population. If the 4 classes of accidents are considered independently, home accidents alone are the ninth cause of death in the United States.

Other considerations add weight to these basic statistical data. For one thing, it is gradually being appreciated that the number of fatal accidents among workers is almost twice as great off the job as on.[39a] Of fatal accidents away from work one-fourth happen at home.

A second feature has to do with the major death rates for accidents of all forms among children less than 1 year of age and for adults past 65 years. Home accidents are the determining factor, for in 1947 no less than 62% of the accidental deaths in the older group were home casualties, while for children aged 0 to 4 years the proportion was 72%.

The data collected by Brown and his associates in Kansas and Nassau County, New York[30c] suggest another important relationship. Excluding infants under one year, where deaths of the sexes were essentially equal, the number of boys dying of home accidents at ages less than 15 years was twice that for girls, with reason to believe that the hours of risk in the home were much the same, and certainly no greater for boys. Males continued to have more fatal home accidents during the productive years, ages 15 to 64, although the numbers were more nearly equal. This occurred despite evident differences between males and females in the number of home hours at risk. A practical significance is brought out when this behavior is translated into working years lost, an excess not compensated by the

greater frequency of such fatal accidents among women at ages past 65 years.

TREND OF HOME ACCIDENTS. The trend of home accidents over the years is necessarily judged on the basis of deaths, because existing data are of that nature. In the early years of the century annual rates for accidents as a whole (Fig. 1) showed little evidence of a trend, but since 1930 the movement has been downward. At best no great improvement has been demonstrated. By excluding the currently introduced factor of motor vehicle accidents, the record is better as shown by the dotted line in Fig. 1, but the gains have been in other fields than home accidents. For 1930 to 1947 the death rates for home accidents in the United States are remarkably uniform, usually about 24 deaths per 100,000 population per year, with a minimum for that period of 23 and a maximum uncommonly beyond 25, the highest rate being that of 29 in 1936. The experience of the present decade, as illustrated in Fig. 2, carries the single satisfaction that no ground has been lost. Home accidents have not kept pace with such improvement as has been shown by accidents in general, by those occurring in industry, nor even with the currently existing rates for motor accidents.

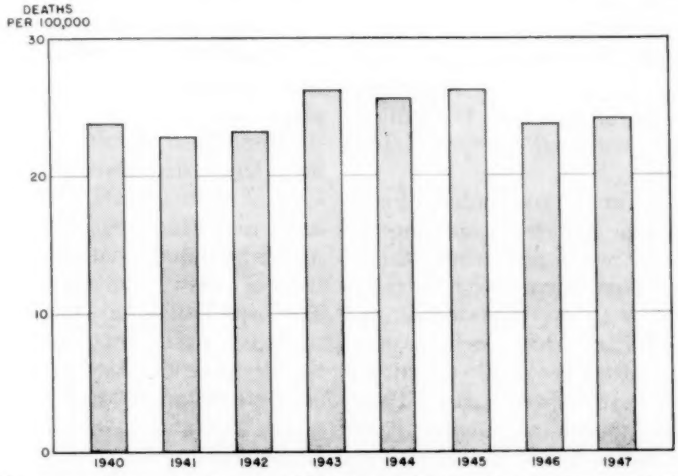

FIG. 2.—Home accidents, deaths per 100,000 population, United States, 1940-1947.[30c]

A PUBLIC HEALTH APPROACH. The need for a more energetic and reasoned advance on the health problem inherent in home accidents is believed clearly demonstrated.[5] This has been interpreted as an obligation of the medical profession, through organized public health agencies and the private practice of preventive medicine. The reason for that opinion rests in the current existence in most health departments of an organization, of facilities, and an experience in visiting the homes of people that is not possessed by other social or adminstrative agencies. Such a direct approach to the home is believed essential in determining first what the problem is and then in developing a preventive program primarily founded on health education. That again is a specialized field of organized public health.

If home accidents are a primary responsibility of community medicine, then it is reasonable to apply the technics[35b] upon which all community health practice is based, whether the

problem is of the communicable diseases, of cancer, diabetes, nutrition or other. In essence, this includes an initial epidemiologic analysis followed by a focal attack on the places and toward the situations where the condition has been demonstrated to be most pronounced. This is accomplished through specific educational procedures and the demonstration of preventive measures by public health nurses or other health visitors in the homes of people. The determination of commonly existing patterns of epidemiologic behavior is the first requisite. In presenting this method of medicine as an approach to the accidents that occur in homes, the suggestion is left that the same procedures may be applied to advantage in other fields of accident prevention not so clearly within the responsibility of the doctor.

The objectives of an epidemiologic analysis of home accidents are simple; first to find out when and where these events take place; secondly, how they occur, which is to say the mechanism involved; and finally, to learn who gets hurt. These matters are vitally practical. Preventive measures are costly. They are time consuming, and interest flags if return is not evident. If universally applied in blanket fashion, they lead to diffuse effort and minimal accomplishment. When deaths from tuberculosis in Detroit were judged some years ago to be beyond reasonable limits, the attack on the disease was not through a city wide campaign, but through search for those fractions of the population contributing in unusual degree to the total tuberculosis of the city. They were found in the population of 3 wards, where intensive control produced a significant improvement in the rates for the city as a whole. The reason for an interest in the patterns of home accidents, or any other community health problem, is to direct available preventive measures intelligently and specifically.

The study of patterns of behavior leads straight to the question of cause, which is more complex than the tangible object so commonly interpreted as the responsible factor in disease or injury, a microorganism in communicable disease or the loose board in a home accident. Rather it is a combination of forces from at least 3 sources, neither one nor the other regularly exerting the principal effect. These are the direct etiologic agent, the character of the host who develops the morbid process, and thirdly, the environment in which both exist, as it influences the interaction of the one with the other.

An organized effort to analyze home accidents as a community health problem comprehensively and on a national scale, has yet to be made. The necessity for repeated reference to estimates will have demonstrated the general lack of factual data. What facts exist have too often been brought together indiscriminately, with no direct objective of answering specific questions. The epidemiologic method of field study is a useful procedure in acquiring the necessary added information. An ecologic interpretation,[22] in terms of agent, host and environment suggests a framework within which to arrange available facts and more important to point to unexplored parts of the problem. A constructive program for prevention depends upon a broad definition of cause. Accidents are believed to be no different from any other mass health problem and hence to conform to general laws of biologic behavior. Similar situations consequently arise from dissimilar causes, they vary in time and in place, and each community needs the specific information derived from a study of local conditions upon which to build a logical and specific program of prevention.

Types of Home Accidents. Whether judged by the approximations of the National Safety Council[30c] or by the

data of Brown[30d] and others, the most common type of fatal home accident is death from falls, since they regularly account for somewhat more than half of all fatalities. Falls on the same level outnumbered falls from one level to another in the proportion of 3 to 2, and together were responsible in 1947 for more than 3 times as many deaths as the next most frequent type of fatal home accident, which was burns, scalds, and explosions. Death from mechanical suffocation surprisingly ranks third among causes of fatal accidents in the home, despite its limitation, 34,500 accidental deaths in the home during 1947.

AGENTS CAUSING ACCIDENTS. The accepted classification of home accidents by type gives all too little information about cause, for the first 3 categories are not descriptive of the things that cause accidents but of the mechanisms by which they took place. Even as mechanisms they lack detail of the activity[39b] in which the person was engaged. A burn may result from conflagration, explosion or scald, from hot liquids or hot solids; the recognition of

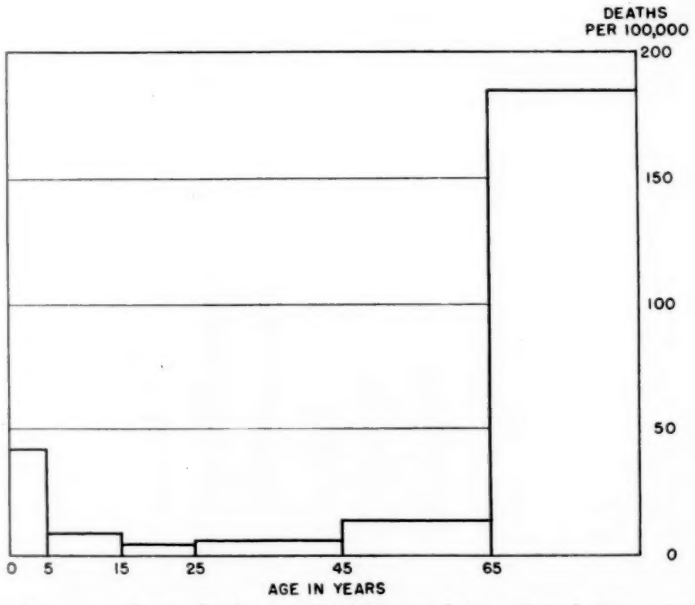

FIG. 3.—Home accidents, deaths per 100,000 population, United States, 1945.[30c]

in an estimated extent of 90%, to infants aged less than one year. More detailed studies[1] have shown a number of such deaths to be properly ascribed to other causes, such as infections, but the recorded total of 1,700 fatalities in 1947 marks this as perhaps the most striking among influences exerted by the age of the patient. Poisons except by gas, poisonous gas, and firearms follow in the order named, with these 6 forms responsible for some 85% of the which of these was the cause has been shown by Schlesinger *et al.*[38] to be a practical consideration in understanding the home accidents of children. Mechanical suffocation may follow from bedclothes or beans; with falls all manner of agents may be considered such as wet or waxed floors, unanchored rugs, loose objects, ladders and stairs. More important is the recognition of faulty design, improper construction or poor repair of objects

about the home as the direct cause of accidents.

Poisons except gas, poisonous gas, and firearms are satisfactory designation of the agent and are susceptible to subdivision and specification. The study of the agent needs still further elaboration, for the things that cause accidents in rural homes are conceivably different from those acting in urban residences, and those concerned with children do not hold for aged persons. So far as known, only the Kansas State Health Department,[26] the Metropolitan Life Insurance Company[6b] and a few others[30a] are collecting data to answer these questions.

ties through the aging process and from disease, and consequently an increased liability to accidental injury. Aside from the deviations in anatomic and physiologic state, inherent differences exist among people, to the extent that some are recognized as unusually susceptible to accidents, a state termed accident proneness. The host patterns of persons who suffer from accidents are thus seen to be of the same general order as those long recognized for many disease processes.

Age. Like so many diseases where the host factor is an important consideration, deaths from home accidents are more frequent at the extremes of

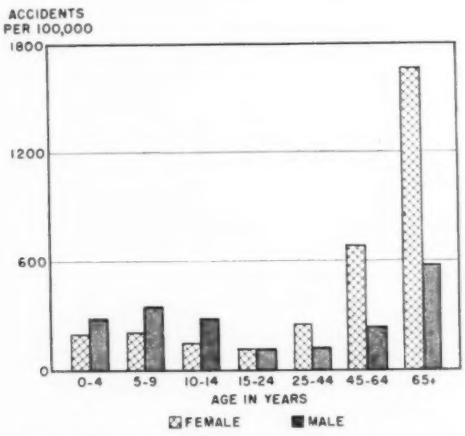

FIG. 4.—Home accidents from falls, per 100,000 population, by age and sex, National Health Survey, 1935-1936.[12]

HOST FACTOR. The common tendency is to look upon the person who suffers an accidental injury as the poor victim of circumstance, and yet the explanation of home accidents is believed more frequently to be found in what are called host factors, within people themselves, than in either the environment or the agents directly concerned. Age alone introduces evident difficulties in the ability of persons to compete with their environment. Infants and young children lack the necessary physical ability and experience. Older persons acquire physical and mental incapaci-

life. The relationship is best defined where separate rates are computed for infants less than 1 year[42b] and for older children aged 1 to 4 years. Death rates for infants are commonly 3 and 4 times greater than for older pre-school children.[42a] For 1945 in the United States (Fig. 3) the home accident rate for all children under 5 years was 42.2. No other age group has the high rate of fatal accidents of persons aged 65 years or more, which for the same year was 185.0 per 100,000.

Reliable data on morbidity of home accidents are almost wholly limited to

facts derived from the National Health Survey[11,12] of 1935-1936. The distributional pattern for total cases by age is similar to that for death from accidents for the country as a whole. Individual types of accidents show pronounced differences. Accidental injury as the result of falls was a relatively minor consideration among children under 5 years, in relation to the total accidents they experienced (Fig. 4). It became an increasingly greater factor with advancing age, and for elderly people was far and away the predominating type of injury. Accidents resulting from cutting and piercing instruments led to an entirely different pattern (Fig. 5), in that children and young adults were principally affected and older persons in appreciably lesser degree.

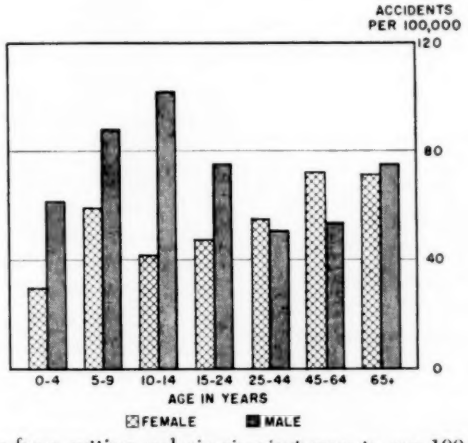

FIG. 5.—Home accidents from cutting and piercing instruments, per 100,000 population, by age and sex, National Health Survey, 1935-1936.[12]

These illustrations suggest the value of examining the types of fatal home accident that predominate at various ages. For 1945 burns were the principal feature at ages 0 to 14 years, and for all other age groups were among the four principal types. Mechanical suffocation and foreign bodies ranked second and third in the youngest age group, 0 to 4 years, but did not appear subsequently among commoner experiences. Firearms were the first cause of accidental injury for the 15 to 24 year group, and rank importantly for the immediately preceding and following divisions. Falls were not represented in the youngest age but assumed increasing importance with advancing age, to become the leading cause of accidental death from home injuries at 45 years and thereafter. These varying distributions give added emphasis to the need for a comprehensive examination of causative factors to include host and environmental influences as well as agent.

Sex. For all groups through 24 years, home accidents are strongly a function of males rather than females, but thereafter females predominate and for elderly people in well marked degree, better than 2 to 1. The distributions that characterize falls (Fig. 4) are fairly typical of the general situation, but individual types of home accidents (Fig. 5) while continuing to demonstrate the principle of a dominance of males are nevertheless subject to quantitative differences.

Race. The national experience in the United States shows somewhat greater accident rates for colored than for white populations,[19] but less than for many mass diseases. They undoubtedly

reflect differences in economic position, geographic distribution and occupational distributions of the races. Selected types of home accidents serve particularly well in demonstrating these differences; for example mechanical suffocation, where the rates for colored infants under one year are twice those for white children of that age.

Acquired Susceptibility. The greater probability of accidents for persons under the influence of alcohol has been studied almost exclusively in relation to motor vehicle accidents. The observations of Joss[25] in Minneapolis show this factor to act also in other types of traumatic injury, but so far as known, its significance in home accidents has not been investigated. Industry has given attention to other forms of acquired susceptibility, such as those resulting from fatigue, impairment of vision, and deficiencies of hearing, but again the situation is unexplored in home accidents.

Inherent Susceptibility. Collected experience, principally in relation to motor accidents[20,31] has demonstrated that certain individuals have repeated accidents, and that multiple accidents by a relatively limited group contribute materially to the whole. This condition, represented by a tendency toward accidents, has been termed accident proneness.[21,28] Neither reaction time, intelligence, physique, nor skill[37] appears to have any part in its origin as an inherent constitutional attribute. It is suggestively distinct from the frequency of accidents associated with an unfamiliar environment, as evidenced by workers undertaking new tasks,[14] or youths learning to drive automobiles, since an improved or extended experience fails to remedy the situation. Such individuals continue to have accidents in whatever occupation they engage and presumably under the varying situations in which they find themselves. The existence of the condition is only to be recognized by the record of past performance, although variously studied by psychiatric methods. Its significance in home accidents has not been investigated.

ENVIRONMENT. The primary classification of accidents on the basis of the places they occur is of itself indication of the importance of environment as a factor in causation. The concept of environment as composed of three major elements,[22] the physical, the biological, and the socio-economic environment, will be followed in interpreting accidents as a result of the competition between man and his environment. The physical environment has to do with matters of climate and weather, of season and topographical affairs, with soil and other physical features of the world where man lives. The biologic component can be taken to include the universe of living things that surrounds man, all else than man himself; while the socio-economic part of environment is that which comes into play through association of man with his fellow man. Environment so considered exerts an influence on disease and injury sometimes through direct action on host or on agent and sometimes on the mechanisms which bring host and agent together or determine their interaction. The results of environmental influences are to be measured by the character of the process that results, by the extent and nature of the frequencies that follow and often by both.

Geographic Distributions. Differences in frequency of occurrence according to geographic regions are characteristic of many mass diseases. Injuries typified by accident show a similar behavior. For all accidents, the western states of America have consistently higher rates than the areas to the east of the Mississippi River, with the mountain states exceeding any other region (Fig. 6). The vacation states of Florida, Vermont and New Hampshire

rank well above the average for the country. Connecticut establishes the best record for 1947 with 50 deaths per 100,000 population, while Nevada with 137.6 is high. Of the 9 standard groupings by which states are commonly distributed for statistical purposes, the middle Atlantic group including New York, New Jersey and Pennsylvania, and the New England states have the best records.

The less comprehensive information about home accidents indicates similar differences in distribution from one part of the country to another. Rates varied in 1947 from 34.5 in Missouri to those of Utah with 16.8 home fatalities per 100,000 population. Little correlation exists between total accident deaths and those for home accidents. The total rate for Utah was high, 82.9, and yet of 27 states separately reporting home accidents it had the best rate. Missouri with the highest rate for home deaths had a wholly ordinary total rate of 74.5, although 46% of reported accidents were in the home. New York had almost an identical proportion of home accidents (45.5%) but the total rate was among the best in the United States (59.7 per 100,000).

The gross differentiation by states scarcely permits the individual community to judge its particular problem of home accidents. Much depends on the concentration and character of the population, as becomes evident when the frequency of home accidents is considered in relation to place of residence, as urban, farm[43] and rural non-farm,[33] for home accidents are clearly a greater problem of urban communities than rural non-farm areas (Fig. 7). The reasons are not well defined but the differences are sufficiently great to suggest material variations from community to community. This has been recognized to the extent that some few cities have determined the frequency of fatal home accidents by subdivision, such as wards or census tracts, and states like Tennessee[40] and Kansas[26] have effected divisions by counties. The result emphasizes the need for individualized information if communities are to apply proper emphasis in control measures.

Largely because of the interest of a few investigators, much is known of the inner structure of the home as an environmental factor in home accidents. The data from Kansas and Long Island[30d] show bedrooms to be the

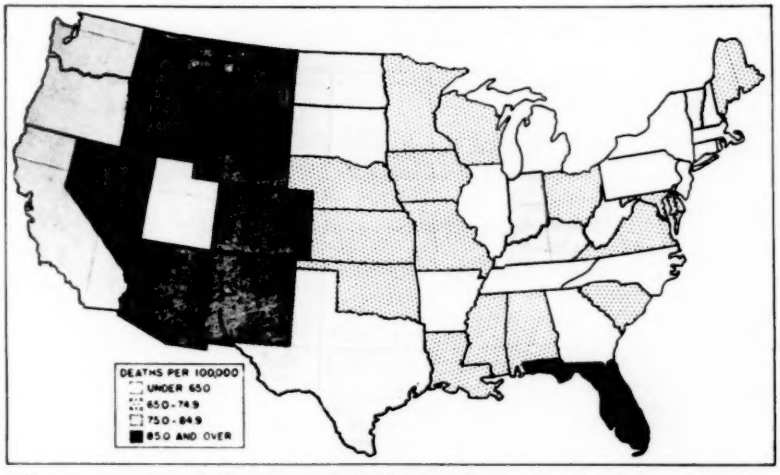

FIG. 6.—Accidental deaths, per 100,000 population, United States, 1947.[30c]

most common location of fatal accidents, because most deaths of infants and persons past 75 years occur there, and for both the total numbers are great. The next most favored site was the yard about the home, and close thereafter the kitchen. Stairs are a natural hazard, with the remaining parts of the home measurably less important. The studies of the Metropolitan Life Insurance Company[39d] led to the conclusion that the kitchen is the most dangerous room in the house. An estimate of 6,000 annual deaths is given. The injuries that occur are likely to be severe and a wide variety of exposures is evident, for this is the factory of the home, the center of domestic activities. The demonstration of the specific kinds of hazard that pertain to various features of home life have permitted direct educational[39c] measures against demonstrated causes and the places they are active.

Distributions in Time. Home accidents when judged by existing frequencies from year to year (Fig. 2) are a steadily recurring phenomenon, corresponding to the endemic behavior of disease. The variations from month to month are likewise minimal as illustrated by the experience of Wisconsin for 1946 (Fig. 8). Although accidents as a whole show no seasonal predilection, specific kinds of home accidents as a whole do experience seasonal fluctuation, for instance the deaths of infants from mechanical suffocation, and from falls at all ages, during the winter months. Generally, the information about distributions in time is none too extensive, especially for non-fatal accidents. Knowledge of home accidents would profit by the methods used in the study of motor vehicle accidents to determine such time factors as the influence of weekends, of holidays, of periods of bad weather, and of the shifting hours of daylight and darkness.

Socio-Economic Environment. Whatever the kind or nature of mass disease or injury, whether it be infectious, metabolic, or traumatic the part exerted by the socio-economic environment is probably the most neglected and underdeveloped of any epidemiologic influence, with accidents no different from any other. Only scattered information can be put together, that arising from the National Health Survey of 1935 being the most constructive.[9,10] The quality of housing, as judged by the amount of income or rental paid, has been repeatedly demonstrated to have an influence on the frequency of both communicable and non-communicable disease. It is not surprising that the same causative influence is shown

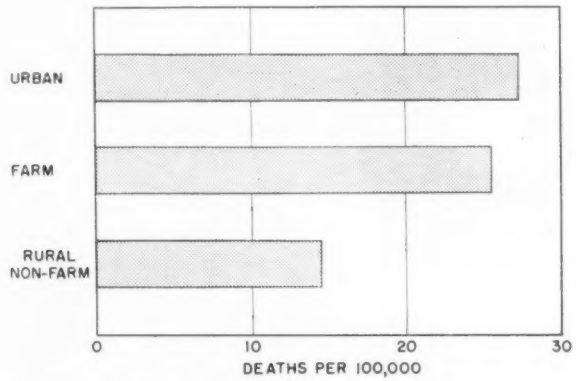

FIG. 7.—Home accidents, deaths per 100,000 population, by place of occurrence, United States, 1947.[30c]

in the frequency of accidents; the lower the standard of housing the greater was the frequency of home accidents. Indeed, many of the physical factors of environment already considered, and those of the host will be seen scarcely to act independently but are representative of a solid admixture with this important component of socio-economic environment.

EPIDEMIOLOGIC METHOD APPLIED. Each of the 3 broad factors in causation has been considered individually to the end of demonstrating principle. But the illustrations themselves and more particularly the concept of epidemiology as medical ecology, show this to be an oversimplification. All 3 factors are intimately interwoven, each influenced by the other. The important consideration is that accidents as a community health problem give evidence of conforming to basic biologic laws, that they are the result of the total forces within a universe, of an ecologic entity, of the competition between man and his environment. This calls for epidemiologic analysis as the practical approach to improved understanding and to a specifically directed prevention.

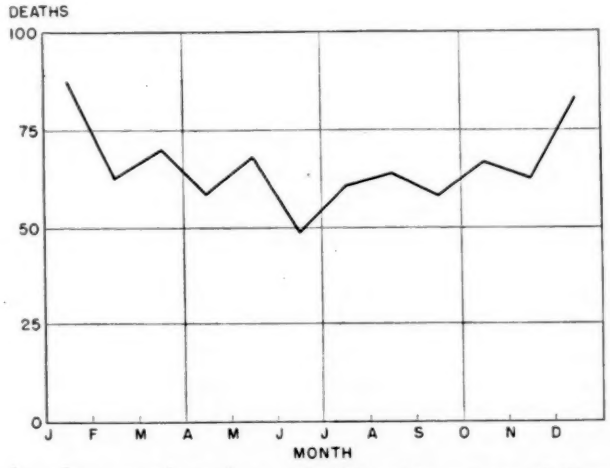

FIG. 8.—Deaths from home accidents, by month, Wisconsin, average 1946 and 1947 (Source: Wisconsin State Board of Health).

A principal difficulty is in unearthing the index case, for case finding through the system of reporting so useful in the study of comunicable disease and some few other conditions, is not available for accidents. Officially filed death certificates relating to accidental deaths are one source of information. Patients admitted to the accident services of hospitals are another. The kind of information basically essential to a comprehensive preventive program is that which relates to the bulk of lesser events, the accidents that result in temporary and often minor disability. This is to be obtained most surely through organized survey and special studies in selected areas. If facilities are not available for such comprehensive investigations a fourth source of index cases is to be had by incorporating the investigation of accidents into the ordinary activities of health departments, where public health nurses and others include a consideration of accidents along with other activities which take them to the homes of people. The choice of method depends largely on the facilities available and the local interest that exists. Something more is needed for an adequate preventive pro-

gram than a knowledge of fatal accidents or of persons seriously injured. The organized survey is the most productive but much can be accomplished by the alternative procedure last mentioned.

Whatever the decision as to the scope of activities deemed practicable, the procedure is the same, an individual case study of the patient, the family group, and the immediate surroundings in which they live. The technic is fundamentally that so well developed for communicable and other diseases. The nature of the accident is determined, the result evaluated in terms of death or recovery, and of temporary disability or permanent defect. The causes are sought through direct investigation of the site of the accident, of the associated circumstances and of the person who was injured. Investigation forms of the type used in Kansas provide a simple means for acquiring and recording the necessary data.

The same considerations of local need and available resources govern the comprehensiveness of data to be collected and analyses to be made. It is within the resources of almost any health department to obtain the simple information about age, date, type of accident, ages involved, and the nature of the injury. Simple correlations may be made of type of accident with age of the patient, with the activity in which he was engaged, of the location within the house, and of the house within the jurisdiction. It is hoped that some few investigators will be able to undertake more comprehensive studies of causation, with as much attention placed on the part played by the host and such fundamental features of the environment as are concerned with socio-economic conditions. It is desirable that these correspond to representative regions within the United States and to varying concentrations of populations in sufficient number to provide the information so clearly needed for a better definition of the laws of accident production.

THE PROGRAM OF PREVENTION. The emphasis which has been given to the epidemiologic approach to accidents has the wholly utilitarian purpose of permitting a more reasonable program of preventive action than is now possible from existing information. Causation needs to be explained, not in the limited sense of the direct agent, but through consideration of the multiple factors inherent in the host, the agent, and the environment. The pattern of study that has been outlined is to that end.

The principal instruments of a preventive program[35a] are rather clearly public health education,[28] the demonstration of existing accident hazards in the home, and direct instruction in the means by which they can be corrected.[6a]

The emphasis thus far has been on what may be done by governmental agencies and official health departments. As with all health activities which involve personal services, the greatest potential promise of accomplishment in accident prevention is through the private practitioner of medicine, in his contact with the families of his community.

A final word about objectives may be useful. Public health activities are directed to the prevention of disease and injury in the community. Circumstances commonly require a similar compromise as in clinical medicine, namely the need to be satisfied with something less than the perfect result; to control and limit disease that cannot be prevented, and when neither is possible, to decrease the costs in terms of permanent defect. All are a positive contribution, although in progressively lesser degree. No assumption is made that all accidents can be prevented, but much can be accomplished in decreasing the health losses from that cause.

No useful additions can be made to the suggestions for home safety activities by local health departments that have been advanced by the Subcommittee on Accident Prevention[3b] of the American Public Health Association. They stress the need for more information, and advice is logically given in procedures that can now be applied with what information is at hand. Only through a better understanding than now exists of what to educate against, and what measures to demonstrate, can these procedures be put into full force.

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PATHOLOGY AND BACTERIOLOGY

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IMMUNIZATION WITH MIXED BACTERIAL ANTIGENS

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THE past war, as was the case with its predecessor, served as a strong stimulus to the widespread investigation of the use of combined antigens for prophylactic immunization. This was to be expected in that the practical advantages to be gained by such procedures in the mass immunization of populations or groups of the population are obvious and become a pressing need under wartime conditions. Studies initiated by World War I were carried on between the wars and this will doubtless prove to be the case once more, and on even a greater scale, since viral and rickettsial infections are now receiving their due attention in this respect. However, it is of value to attempt to measure and report the progress made after a period of activity in any field, and this would appear to be an appropriate time to do so in regard to work dealing with the use of mixed bacterial antigens.

The initiation and study of the use of combined bacterial antigens for prophylactic immunization was for many years retarded and hampered by widespread acceptance of the theory that such efforts would fail to produce a good response to each component inoculated, or that the response to each component would be much less satisfactory than that following their separate injection. This theory as to the "competition of antigens" had its basis in the work of Michaelis[24] who in 1904 demonstrated that the injection of untreated blood serum resulted in only slight antibody production against albumin, but good precipitin for globulin. Immunization with the albumin fraction alone resulted in a large preciptin production. Support for this attitude was provided by Friedberger[15] the same year, using combined typhoid and cholera vaccine, for he claimed that this resulted in cholera antibody formation being 6 to 37 times lower than when cholera vaccine alone was employed. More recent evidence of the same nature has been provided by Zlatogoroff *et al.*[41] in 1929 and by Scheibel[36] in 1944. Their experiments were carried out in guinea pigs using diphtheria and tetanus toxoids and the conclusion was that immunization with 2 antigens would result in a lowered response to at least 1 of them. However, this effect was most noticeable with small doses and few injections and raises the possibility that the different response was essentially due to differences in threshold rather than competition between antigens. Scheibel also was of the opinion that his findings did not present a complete barrier to human use of such mixtures, in that even with some reduction in antibody formation, the amount produced for both

components was sufficient for effective protection.

These studies cannot be disregarded, but at the same time the great majority of reports do not demonstrate adverse results from the inoculation of combined bacterial antigens. In fact the reverse is the case, for more recently the most striking feature of such studies has been the discovery that the response to some or a number of components in a mixture will be actually enhanced by their employment as a constituent of a mixture rather than as a single entity for immunization.

There would appear to be some dispute as to which worker should receive credit for initiating the long series of studies dealing with the use of multiple antigens in prophylactic vaccination. On the evidence available, Castellani[8] would appear to have earned this distinction, for in a paper published in 1915 he cited publications by him in the preceding 15 years in this field. In 1901-02 he claimed to have demonstrated that rabbits inoculated with several species of bacteria developed agglutinins for each to as great an extent as control animals receiving only one species by inoculation. This result led him to introduce the use of a combined typhoid, paratyphoid A and B vaccine in Ceylon in 1905 and to the later addition of killed cholera vibrios to the mixture. By 1915 it was possible to report[7,8] that some 170,000 individuals had been immunized with this "tetravaccine" in Serbia. Castellani did not restrict his investigation to the vaccine components already described, but also investigated combinations of up to 6 constituents and stated that some 14 combinations of 2 or more antigens had been used in humans. In 1916 a similar study was reported by Weber,[39] who claimed that immunization with mixed cholera-typhoid vaccine produced as high agglutinin titers for both antigens as were obtained in controls receiving separate inoculations of each antigen.

Although these pieces of work must receive historical precedence, the most noteworthy attempt to demolish the theory of antigenic competition came from a series of reports by Ramon and Zoeller[32 a-f] in 1926 which were summarized by Ramon in 1939.[33] This work showed that the inoculation into animals of a non-specific adjuvant such as tapioca, calcium chloride or alum to an antigenic substance such as diphtheria toxoid resulted in the host giving a much improved response to the antigen as measured by specific antibody production. This observation was then applied to animals, and later to humans, in the inoculation of such unlike materials as diphtheria toxoid and typhoid vaccine. It was then established that satisfactory polyvalent immunization could be produced by the simultaneous inoculation of typhoid vaccine, diphtheria and tetanus toxoids. Similar studies were reported in 1935 by Ando and Nagata[1] who found that alum precipitated scarlet fever and diphtheria toxoids produced in rabbits as good a response in combination as alone; and in 1940 Schutze[37] who reported that in guinea pigs the antigenic potency of alum precipitated diphtheria toxoid and pertussis vaccine was not impaired by combination in a mixture for immunization. The possibility that mixing of antigens might have a deleterious effect upon the components of the mixture was shown to be without foundation, at least in regard to a mixture composed of the organisms responsible for typhoid and paratyphoid fevers A, B and C when combined with tetanus toxoid and stored for any reasonable period of time.[17]

These and similar studies have provided the experimental basis for the intensive investigation of the use of combined antigens for active immunization against bacterial diseases in which this approach has proved either

feasible or justifiable on the basis of need for such protection. Although many combinations of such bacterial antigens have been subjected to investigation, the major attention of the past two decades has been directed to certain specific diseases, namely: the typhoid and paratyphoid fevers, diphtheria, whooping cough and tetanus. At this time it is proposed to present evidence that has been produced in regard to the status of combined immunization in each of these infections of major interest to medicine on this continent and to discuss some of the general problems of combined immunization that have arisen as an unforeseen consequence of studies more narrowly directed.

The customary age distribution of cases in the diseases just mentioned has tended to divide immunization studies rather sharply into 2 categories. Those concerned with prophylaxis against the typhoid and paratyphoid fevers have dealt with adult groups; those dealing with diphtheria and whooping cough have been concerned with the infant and child elements of the population. The original conception of tetanus as an adult hazard resulted in its being of concern to the first group, but a more recent appreciation of the significance of this disease in childhood has had the effect of sharing of interest in this disease by all concerned with combined immunization.

The tremendous value and great effectiveness of typhoid vaccination was firmly established in World War I, although extensive British experience with typhoid vaccine had begun with the South African War. At that time the results were not convincing in regard to lessening of incidence of enteric infection in the recently immunized troops, but the case mortality rate was reduced from 16.6% to 8% in that group as compared to uninoculated controls. A very striking reduction of both incidence and mortality from enteric fever was demonstrated in the period 1909-1913 when British troops serving in India were practically all inoculated with typhoid vaccine. Very complete records exist of British experience with typhoid and T.A.B. (typhoid, paratyphoid A, paratyphoid B) vaccine in the first World War.[29] At the beginning of the war in 1914 only some 30% of troops had received a single inoculation of typhoid vaccine, but this was gradually increased to over 90% by the end of the next year. Early in 1916 T.A.B. vaccine was introduced and its use in 2 doses of 0.5 cc. and 1.0 cc. at 10 and 14 day intervals replaced simple typhoid vaccine for the remained of the conflict. During 1915, when protection against only typhoid fever was provided, the incidence of this disease in those immunized was less than one-tenth that occurring in the uninoculated and there was evidence of a considerable degree of protection against paratyphoid fevers A and B as well, particularly in regard to mortality from those diseases. In the final year of the war, when fully 95% of some 2½ million men were fully protected with T.A.B. vaccine, the incidence of enteric disease was reduced to only 376 cases.[38] French and American experience provided confirmation for these striking results.

The satisfactory results thus demonstrated were more than duplicated in World War II. In a recent report[28] it has been stated that fewer than 50 cases, with only 2 fatalities, occurred in an army of over 3 millions.

The widespread adoption of typhoid vaccine, later followed by the incorporation of the organisms responsible for the paratyphoid fevers, was a major development. Although it is true that such vaccines are mixed vaccines in every sense of the word, the fact that the elements composing them were bacterial cells of somewhat similar morphological and cultural characteristics and the causative agents of

clinically similar diseases tended to blunt the impact of this important innovation; though it probably prepared the ground for the acceptance of large-scale use of more unusual mixtures for prophylaxis of other diseases recognized as being of major significance in military medicine. This further step could only be taken if it were possible to demonstrate that the effectiveness of vaccination against the enteric infections was not impaired by the new constituent of the mixture.

The importance of diphtheria as an endemic disease in France led to the introduction of compulsory immunization for diphtheria among French troops in 1931 and studies were soon undertaken to demonstrate the possibility of combined immunization. The results were satisfactory and in one study[12a] it was reported that the attack rate of diphtheria per thousand men was reduced from 10.7 in the unprotected to 0.84 in those immunized with the combined material. As a consequence of these and other findings[12b,34] it was decided that combined immunization should be the recommended procedure for primary immunization of recruits.

As was to be expected, the importance of tetanus greatly outweighed that of diphtheria in the eyes of those concerned with active immunization of adults, and this was particularly the case in regard to members of the armed forces. As a consequence, the vast majority of studies dealing with the combination of typhoid-paratyphoid vaccine and other antigens have been concerned with a mixture incorporating tetanus toxoid as a major constituent. The value of tetanus antitoxin as a prophylactic agent was shown in World War I when its introduction resulted in the incidence of tetanus falling from 8 to 1 per thousand wounded.[6] However the demonstration that active immunity could be established by the use of tetanus toxoid encouraged studies of this approach to the problem between the wars, since there were great disadvantages to any plan of prophylaxis which placed complete reliance upon the administration of passive immunization to wounded in the field. Active immunization would also tend to eliminate the problem created by hypersensitivity to horse serum. At the beginning of World War II sufficient work had been reported[9, 19b,22,34] to justify the conclusion that tetanus toxoid could be combined with other antigens for effective immunization against all components of the mixtures. Reports have since appeared as to the great effectiveness of active immunization against tetanus under war conditions. Boyd states[6] that in the British Expeditionary Force of 1939-40 in Europe there were 7 cases of tetanus in the non-immunized 10% and no cases in the immunized 90%. A quotation from a paper by Montgomery[28] is even more striking: "Perhaps the most dramatic advance in preventive medicine was encountered in the protection given by tetanus toxoid. It was given to all Canadian and American soldiers at the same time as the T.A.B. vaccine. To my knowledge, no authentic case of tetanus developed in the Canadian Army overseas, and Colonel Wm. Middleton, Chief Consultant in Medicine, European Theatre of Operations, U. S. Army, is authority for the statement that only 1 instance of tetanus occurred in the American Army. The Nazis afforded the perfect control. Only the Luftwaffe and certain paratroop elements received tetanus toxoid. Of the unprotected German prisoners-of-war, hundreds developed tetanus and scores died in Allied hospitals." To sum up, one may say that the incidence of tetanus was reduced to negligible proportions by active immunization, though it is still a matter of some dispute as to whether the wounded man should also receive tetanus antitoxin or complete reliance be placed upon a

reinforcing inoculation of toxoid at the time wounding occurs.

Despite the significance attached to tetanus as a problem of military medicine, there has been increasing attention paid to its occurrence among civilian groups. In 1938 Cooke pointed out[10] that in 1930 the mortality rate from tetanus in the United States was 1.1 per 100,000 of population and that, although children constituted less than 30% of the population, more than half the tetanus deaths were in childhood. This statement was at variance with the conventional belief that tetanus was a hazard of ordinary life only when occupation, such as farming, created a special need for protection. The fact that reliance could not be placed upon routine use of tetanus antitoxin at the time of injury was stressed by Pratt[31] in an investigation of 56 cases of tetanus. He found that in 60% of these patients the original injury was of such a nature that prevention would not be achieved by the application of conventional measures in that the injury was not appreciated or was of such a nature as not to demand prophylactic procedures. However, acceptance by the medical profession of these views would by itself achieve little, since it is unlikely that the general population would accept routine active immunization procedures specifically directed against tetanus in view of the relative rarity of this disease in civilian life. At the same time, the general acceptance of prophylactic immunization against certain other diseases affords an opportunity for production of the desired protection against tetanus provided tetanus toxoid can be administered simultaneously and without deleterious effect upon the other antigenic components of the mixture.

The need for exact information on this point has stimulated a number of studies dealing with the effectiveness of tetanus toxoid when combined with diphtheria toxoid and pertussis vaccine, the antigens routinely used in the prophylactic immunization of infants and children. Results of studies reported by Peshkin;[30a,b] Bigler and Werner;[3] Deamer *et al.*;[11] Lapin;[21a,b] and by Miller and his associates[26,27] have all demonstrated a satisfactory response to tetanus toxoid and no appreciable interference with the other components of the various mixtures employed. The studies of Peshkin[30a,b] are of particular interest in that they deal with the response to such active immunization by a group of 186 allergic children who might be expected to present a serious problem were the need for passive immunization to occur in the future. Some 94% responded satisfactorily to 2 inoculations of the combined alum precipitated diphtheria and tetanus toxoids used in these studies and of the remaining 6%, all but 1 child gave a satisfactory response to a third inoculation. Even after 2 years, nearly half of these children had an adequate level of tetanus antitoxin and there is no question but that a reinforcing inoculation would result in a good response from this group on the basis of results reported by Bigler and Werner[3] and Miller and Ryan,[27] when the response of the immunized child to such a stimulus was measured.

The general acceptance of the value of diphtheria toxoid demanded thorough investigation before the addition of other antigens to this material could be advocated. It has long been held that a combined immunization against diphtheria and whooping cough would be most desirable, if it was practicable, and the more recent interest in active immunization against tetanus has reinforced the need for investigation of this problem. The early work of French investigators;[12a,b; 32a-f] using a combination of diphtheria toxoid and typhoid vaccine was a hopeful augury for this approach to the needs for active immunization in the infant and child population. In 1934 Ingels[18] confirmed

French experience by showing that 90% of a group of 3,000 elementary school children had been rendered Schick negative by a course of combined diphtheria-typhoid immunization. Bordet in 1936[5] was the first to report the use of a mixure of diphtheria toxoid and pertussis vaccine; but he provided no data on immunity tests for either disease, nor did he report clinical evidence of protection. Since 1942 a number of studies concerning the combination of diphtheria toxoid with other bacterial antigens have appeared and certain of these can be referred to as illustrative of the results obtained.

Kendrick[20a,b] has reported extensive field studies involving more than 6,000 children in which pertussis vaccine has been used alone and in combination with diphtheria toxoid. Her results indicated a satisfactory response for both antigens, whether administered singly or combined, based upon diphtheria antitoxin titers and, in the case of pertussis vaccine, upon both laboratory determinations and actual incidence of whooping cough in immunized and control groups of children. These results have been supported by Lapin[21a] who administered a combination of fluid diphtheria toxoid, alum precipitated tetanus toxoid, pertussis vaccine and pertussis toxin to 78 infants of 6 to 9 months of age. Deamer *et al.*[11] immunized over 600 infants with combined diphtheria and alum precipitated tetanus toxoids and found that, under the conditions established, 96% were rendered Schick negative. Sauer *et al.*[35] carried out studies using mixtures of both plain and alum precipitated diphtheria toxoid and pertussis vaccine. The response, as judged by negative Schick tests and strongly positive *H. pertussis* complement fixation tests, was very satisfactory and gave strong support to the use of the combined product for immunization. The response to the alum precipitated mixtures was somewhat better, particularly as regards pertussis antibodies, but the greater severity of reactions would tend to make the plain mixture the product of choice. Miller and his associates[26,27] have reported the use of a combination of aluminum hydroxide adsorbed diphtheria and tetanus toxoids containing pertussis vaccine in a group of 126 children. These have shown an extremely good response to the toxoid components of the mixture and a fairly satisfactory response to the pertussis vaccine, which was improved in a second group of 103 children by increasing the dosage of that component. In 1946 Foley[14] reported a study covering a 3 year period in which more than 38,000 children of 6 months to 10 years of age were inoculated with combined diphtheria toxoid and pertussis vaccine. The protected group in the population showed a tremendous reduction in the morbidity from both diphtheria and whooping cough as compared with the non-protected population and there was no mortality from either disease in those immunized. Some 3,000 of those immunized also received a reinforcing inoculation and no case of either disease was known to have occurred in this group. The results of this extensive experience, under field conditions where both diphtheria and whooping cough were prevalent, allowed the conclusion to be made that the combined immunization does not lower the protection afforded by diphtheria toxoid and that it gives appreciable protection against whooping cough. Recent studies by Bell[2a,b] in which he used an alum precipitated mixture of diphtheria toxoid and pertussis vaccine have confirmed this impression of immunizing effectiveness, although here again the protection established against whooping cough is not as effective as that produced against diphtheria.

A matter of some importance in regard to combined immunization against diphtheria and whooping

cough has to do with the need for protection against the latter disease at the earliest possible opportunity. The importance of whooping cough as a cause of death in the first year of life makes it imperative to establish immunity at an earlier age than has been customary in the past for diphtheria toxoid in most public health programs. Some doubt has been expressed as to the effectiveness of active immunization when carried out before an infant is at least 6 months of age. In this respect, the report in 1948 of Fleming *et al.*[13] showing a satisfactory response to immunization in a group of infants averaging 4 months of age would appear to be of significance as indicating the possibility of producing active immunity against whooping cough at a time when it is of greatest value; and yet not interfereing with the more widely accepted value of active immunization against diphtheria by combined inoculation at this early age.

At this point, consideration has been given to those procedures carried out to produce effective active immunization against two or more bacterial infections by combination of immunizing materials. In the course of these studies a number of observations of a more general nature have been made which demand attention in that their importance is such that they will very markedly affect any attempt to introduce combined immunization as an acceptable, routine procedure for general use in the population.

One such matter, of concern to physicians and laity alike, is the effect of mixing of antigens upon the severity of reactions, either local or constitutional, which may be expected to occur in patients receiving such materials. In 1937 Jones and Moss[19a] demonstrated a satisfactory immune response in 41 adults who received 2 inoculations of combined alum precipitated diphtheria and tetanus toxoids; but they felt that the reaction to the combined material was more severe than when the constituents were employed individually. Peshkin, in his study[30b] of 65 allergic children, stated that the incidence of local reactions was about 25% with repeated inoculations of combined alum precipitated diphtheria and tetanus toxoids, but that no allergic reactions such as urticaria or asthma were encountered. Sauer *et al.*[35] reported the occurrence of a "sterile abscess" in 2% of injections, using combined alum precipitated diphtheria toxoid and pertussis vaccine. They felt that this was reason for advocating the use of the plain mixture, even at some expense to the immune response. However, these reports of increased severity of reaction are definitely in the minority.

Sacquépée *et al.*[34] reported absence of marked reactions in seven thousand adults who received combined inoculation against typhoid and paratyphoid fevers, diphtheria and tetanus. MacLean and Holt[22] felt that injection of tetanus toxoid and T.A.B. vaccine produced no more severe reactions than would result from the use of the vaccine alone. Bigler and Werner[3] had the same opinion concerning the addition of tetanus toxoid to diphtheria toxoid. Chen[9] found that the inoculation of combined T.A.B. vaccine and fluid tetanus toxoid was less irritating, and a more efficient antigen, than alum precipitated tetanus toxoid in guinea pigs. Lapin,[21b] Deamer *et al.*[11] and Fleming *et al.*[13] all report the absence of severe reactions in infants and children receiving various combinations of antigens. This would appear to be sufficient evidence to justify the belief that mixing of antigens does not increase the incidence or severity of reactions to the products and, therefore, will be no barrier to their adoption for general use.

A question of greater interest has to do with the rapidity and duration of response to combined antigens as com-

pared with that produced by the individual components of such mixtures. That is, will the reduction of material inoculated of each constituent in a mixture, or the necessity of altering the spacing or number of inoculations usually found desirable, have an adverse effect upon the immunity level attained for each component of the mixture? The evidence available provides reassurance on this important matter.

MacLean and Holt[22] report that when tetanus toxoid is combined with T.A.B. vaccine and given in 2 inoculations spaced a month apart, the response to the T.A.B. vaccine was just as satisfactory as when T.A.B. vaccine is administered at the customary weekly interval. Bell has shown[2a] that failures to immunize children with alum precipitated diphtheria toxoid, given in 1 or 2 inoculations, were 3 times as great as in the case of children who received the same number of inoculations of a combination of alum precipitated diphtheria toxoid and pertussis vaccine. The same picture of greater effectiveness for the combined product could be related to the age at which the children were immunized; for children, who received 2 inoculations of the combined product before they were 6 months of age, had fewer failures to immunize against diphtheria than children who received diphtheria toxoid alone at any age up to 23 months. The large-scale field study of Foley[14] provides strong evidence that combined immunization against diphtheria and whooping cough does not lower the protection against diphtheria which could be effected by diphtheria toxoid alone, nor does it interfere with the response to subsequent reinforcing inoculations. Various studies[25,27] have shown satisfactory protection against whooping cough over a lengthy period of time following combined immunization and similar reports have appeared[3,11,30a,b,34] in regard to the level of tetanus antitoxin established by this method.

The early opposition to the use of combined antigens, provided by the supporters of the theory of antigenic competition, was swept aside when it was demonstrated that concurrent immunization against 2 or more antigens could be readily achieved. However it has become possible to adopt a more positive approach to the use of combined antigens in the past 2 decades as a consequence of the introduction of the hypothesis of antigenic synergy. The experiments of Ramon and Zoeller[32e] with mixed vaccines provided the basis for this new approach, in that the results obtained with combinations of antigens were better than could be expected from the individual components of such mixtures. Support for this viewpoint was furnished in 1928 by Weinberg *et al.*[40] when they immunized guinea pigs with mixtures of 2 species of clostridia and found that the antibody titers were only slightly lower than those observed in controls which had received considerably larger doses of single antigens. It would be reasonable to assume that there is a physical limitation placed upon such synergistic action and in 1941 Bjorneboe[4] produced evidence that this was the case. After demonstrating that rabbits could produce specific antibodies for pneumococcal types inoculated as mixtures containing up to 8 different types, he showed that animals immunized with a combination of 3 types gave higher titers for the individual types than did animals receiving 4 to 8 types.

More specific information concerning this synergistic effect of mixed antigens has appeared in recent years. Chen in 1933 had shown[9] that the combination of tetanus toxoid with T.A.B. vaccine had given a better response than is obtained with tetanus toxoid alone. MacLean and Holt in 1940[22] found that this increase was 5 fold. Reference has already been made to

the work of Bell[2a] who reported that a mixture of diphtheria toxoid and pertussis vaccine resulted in fewer failures to immunize than was the case with diphtheria toxoid alone, and that this enhancement of antigenicity was particularly well shown in young infants. Miller and Ryan,[27] using combined aluminum hydroxide adsorbed diphtheria and tetanus toxoids with pertussis vaccine, found a satisfactory response to all components; and the prolongation of a high degree of immunity was very striking in this study, for those retested 2 to 4 years later were all Schick negative and 98% of those tested at this time showed levels of one-tenth unit or more of tetanus antitoxin.

Experiments designed to investigate this synergistic aspect of combined immunization in a quantitative manner are not numerous. Mathieson in 1942 reported[23] that in guinea pigs the antigenicity of diphtheria toxoid was increased by administration in combination with pertussis vaccine. In rabbits, the same product resulted in as good a production of agglutinins for *H. pertussis* as did pertussis vaccine alone. In 1947-48, Greenberg and Fleming described[16a,b] a series of experiments carried out in guinea pigs, of sufficient number and with adequate controls for the constituents of various combinations of antigens, designed to allow for statistical analysis of the results. For example, 4 mixtures of diphtheria toxoid and various concentrations of pertussis vaccine were each inoculated in 3 different amounts and the response to the diphtheria toxoid of each mixture compared with that given by control animals receiving only toxoid of identical strength. The results showed a consistent increase in the immunizing power of the diphtheria toxoid when it is inoculated simultaneously with increasing numbers of *H. pertussis* organisms; and the increased efficiency ranged from 216% to 405% as compared with the controls. The response to diphtheria toxoid was determined by Schick testing 19 days after a single inoculation. On this basis it could be stated that when the concentration of pertussis organisms usually found in commercial preparations is added to diphtheria toxoid, the immunizing efficiency of the latter is at least doubled. When a third antigen, such at tetanus toxoid or scarlet fever toxin, is added to this combination, the immunizing efficiency of the diphtheria toxoid is increased 5 to 10 fold. As might be expected, the potentiating effect of the presence of other antigens was not demonstrated for the response to pertussis vaccine itself, since that agent is already in a particulate state. Additional studies of the same character carried out in infants[13] confirmed these quantitative results in so far at least as combinations of diphtheria and tetanus toxoids and pertussis vaccine are concerned.

It would seem possible to state that at this time there is general acceptance as to the feasibility and value of combined immunization for prophylaxis against a number of bacterial infections of major importance in all segments of the population. It is also quite certain that a great deal yet remains to be done in order that such procedures may be introduced in a way to confer the greatest possible benefits from their use. Adequately controlled studies must be undertaken to establish size and number of inoculations and to determine the time element that provides for the most effective response to such inoculations. The discovery of antigenic synergy requires further investigation, since it provides a most hopeful indication that smaller dosage will result in a satisfactory immune response and will, at the same time, reduce the possiblity of severe reactions in the immunized individual. Further information is needed concerning the advantages and limitations of plain, alum precipitated, and aluminum hydroxide adsorbed products for use in combined form.

The work reported to date has covered such a wide field, and has been carried out under such different conditions, that information on many important aspects of combined immunization is scanty or altogether lacking. This same set of circumstances has made comparison of experimental results very difficult or unsatisfactory. However, the stage of investigation has now been reached where intensive and adequately controlled studies of more limited problems can be undertaken and it is certain that a definite advance in the use of combined bacterial antigens will thereby result.

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PROCEEDINGS OF
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA
SESSION OF DECEMBER 21, 1948

The Response Pattern of the Pacinian Corpuscle. DONALD SCOTT, JR., M.D., Ph.D. (Johnson Foundation for Medical Physics, Univ. of Penna.). It is possible to dissect the Pacinian corpuscle in the mesentery of the cat so that electrical records of its activity are easily obtained while it is still receiving its normal circulation. Stimulation of this corpuscle can be effected by means of: (1) a steady pressure of 5 to 30 mg. with a glass rod, or (2) a vibratory stimulus which may be in the form of an audible tone, or (3) a change in the electrolyte balance of the cell fluid by such means as application of isotonic sodium citrate. The response to such stimulation of a single corpuscle is in the form of a series of impulses which are each separated from the next adjacent impulse by an interval which is about 3 to 5 m.secs. in length or some simple multiple thereof. This interval corresponds to that found by Brink in peripheral nerve when treated with isotonic citrate solution and may be regarded as a fundamental oscillatory variation in the excitability of the corpuscle. Careful examination of the record between two impulses separated by several fundamental intervals shows small potentials which appear to be subthreshold electrical changes in the corpuscle having the same fundamental interval as the conducted responses. The length of this interval can be altered by the strength of stimulation: it being shortest when a strong stimulus is applied and the response rate is high. Using a pure tone from an oscillator it is possible to map the response threshold of the corpuscle as it varies with frequency and it is found that there is a sharp "valley" in this curve at a frequency corresponding to the length of the fundamental interval and a second "valley" at a frequency corresponding to the first harmonic of this fundamental frequency. Using a very strong stimulus it is possible to obtain impulses separated by less than the fundamental interval (in fact these appear to be separated by only the refractory period of the corpuscle) and in this case it appears that with strong stimuli one can produce two responses during a single fundamental interval.

Do Anesthetics Depress Nerve Cells by Depressing Their Metabolism? Observations on Sympathetic Ganglia. MARTIN G. LARRABEE, Ph.D. (Johnson Foundation, Univ. of Penna.). Relationships between the effects of anesthetics on the metabolism and on the functioning of nerve cells were investigated by simultaneous measurements of oxygen consumption and synaptic transmission by sympathetic ganglia of rabbits.

A ganglion was excised and placed in flowing solution in a small lucite chamber. Rate of oxygen consumption was determined by measuring with a polarized platinum electrode the rate of fall of oxygen concentration in the chamber when the flow of solution was stopped. Synaptic transmission was measured by the height of the action potential in the postganglionic nerve caused by impulses discharged from ganglion cells in response to volleys of preganglionic nerve impulses.

Chloretone, nembutal, ethyl alcohol, and several higher alcohols were all able to depress oxygen consumption, but this occurred only at concentrations higher than those required to depress synaptic transmission. Ethyl urethane slowed the oxygen consumption by a small amount, the magnitude of which

did not increase as the concentration was raised from levels which did not effect transmission up to those which blocked it. As a control it was shown that rate of oxygen consumption could be considerably reduced by sodium azide without depressing synaptic transmission.

These facts are difficult to reconcile with the hypothesis advanced by others that anesthetics depress the functional capacity of nerve cells by interfering with their metabolism.

Oximeter Control of the Induced Anoxemia Test of Cardiovascular Function. RAYMOND PENNEYS, M.D., and CAROLINE BEDELL THOMAS, M.D., (Depts. of Prev. Med. and Med., Johns Hopkins School of Med.). Further experiences with oximeter control of induced anoxemia[1] are presented. Analysis of the inspired gas[2] showed that the oxygen concentration had to be almost constantly altered to maintain a given arterial oxygen saturation. The oxygen concentration necessary to produce a saturation of 75% varied from 8.3 to 12.4%. To keep one particular subject at 80% arterial saturation, for example, 9.5% O_2 was necessary at one moment and, 13.5% O_2 just a few minutes later.

This method of producing a constant arterial oxygen saturation by the administration of a gas of variable O_2 concentration was used in 92 anoxemia tests on 72 normal persons. Practically all subjects could be induced to the desired levels of anoxemia at a standardized rate: 5 minutes from 95 to 80%, 1½ minutes from 80 to 75% or from 75 to 70%. The subject was then maintained at each level for the desired length of time. Blood pressure, pulse and electrocardiogram were taken at each level. Maximum RS-T change at 80, 75 or 70% was 1 mm. in any one lead or 2 mm. for Leads 1 to 4. The T wave was depressed with progressive lowering of the saturation. The degree of the depression correlated well with the level of saturation. T 3 or 4 was occasionally reversed. No "positive" tests for coronary disease were obtained. The heart rate increased with lowering arterial saturation; the increase was greater and more consistent as 70% was reached. The average systolic and diastolic blood pressure increased slightly at all levels of saturation. The physiological advantages of oximeter controlled anoxemia are discussed.

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2. In conjunction with Ross L. McLean, M.D., Dept. Med.

Relation of Number of Metastases to Size, Number and Duration of Primary Tumors. I. ZEIDMAN, M.D. (Pathology Dept., Univ. of Penna. Med. School). Experiments were designed to determine the effect of primary tumor size, number of tumors, and duration of tumor on the number of metastases. A transplantable fibrosarcoma, T-241, was inoculated into one or both flanks of C-57 mice. Pairs of mice bearing single tumors and pairs bearing double tumors were sacrificed at various intervals between 9 and 26 days after the inoculation of the tumor.The tumor volumes were measured and the lung metastases were counted. There was no significant relationship between number of lung metastases and primary tumor volume or number of primary tumors. The correlation between number of metastases and duration of primary tumor growth was strongly positive.

BOOK REVIEWS AND NOTICES

THE DIGESTIVE TRACT IN ROENTGENOLOGY. By JACOB BUCKSTEIN, M.D., Ass't Prof. of Clinical Medicine, Cornell Univ. Med. Coll. Pp. 889; 1030 ills. Phila.: J. B. Lippincott, 1948. Price, $16.00.

THIS book is one of the best that I have had an opportunity to review. The author, in his first book, did a magnificent piece of work and in this instance he has improved on it in many ways. Most of the commonly known facts concerning the gastro-intestinal tract are discussed as well as many of the rare conditions. This book is the type of book that should be on the desk of every radiologist and every gastro-enterologist. Many of those interested in general medicine will find it informative.

The reviewer has only one suggestion—that a chapter on the technique of fluoroscopy and radiography as it concerns the gastro-enterologist be included in further editions. In this detailed comments on protection of the patient and of the operator from over-exposure should be included. A book such as this one will have wide use and many people will attempt to do fluoroscopy who are not adequately informed about its dangers. The print is excellent and the illustrations are good.

E. P.

DRUG RESEARCH AND DEVELOPMENT. Edited by AUSTIN SMITH, M.D., Director, Division of Therapy and Research, American Medical Association, and ARTHUR D. HERRICK, Food and Drug Consultant, Attorney, and Author. Pp. 608. New York: Revere, 1948. Price, $10.00.

TODAY few persons interested in the development of drug therapy have a clear picture of the operations involved in formulating, testing and marketing a new formula. To make available a reasonably detailed survey of these steps in drug research and development, the editors of this volume have called upon their own knowledge and that of 16 other recognized experts in fields ranging from pharmacology through patent and trademark law to advertising and price maintenance. For example, M. L. Tainter presents in 33 pages an excellent discussion of laboratory research, including purpose, objectives and general plan of organization, the types of research and development and an able defense of the use of animals in research.

At the other end of the line, C. S. Downs explains in 42 pages the objectives of advertising, the media used (sample, direct mail, and professional journals), the methods of determining proper appropriations, and other lesser aspects.

The authors are to be complimented for the manner in which they have presented the over-all picture of each topic as well as brief discussions of its most important procedures and problems. Their success can be attributed to their conscientious avoidance of generalities. The book is enthusiastically recommended to anyone desiring a balanced background in the many operations which make a modern drug available to the physician.

F. B.

SYMPOSIA ON NUTRITION. Vol. I. NUTRITIONAL ANEMIA. Edited by ARTHUR LEJWA. Pp. 194. Illustrated. Cincinnati, Ohio: Robert Gould Research Foundation, 1947. Free, on request.

THIS volume comprises a brief preface by the Editor, Introductory remarks by E. V. McCollum and chapters by Wintrobe, Elvehjem, Darby, Zuelzer, Schultze, Cartwright, Moore, Guest, Sebrell and Vilter each representing a contribution to a Symposium on Nutritional Anemia organized by the Gould Foundation and held in Cincinnati under auspices of The College of Medicine of the University of Cincinnati in October 1947. It is an excellent summary of the known data at that time. The symposium was presented a few months too soon to include notice of "B-12" which constitutes an important new chapter for the next edition. This little volume is unreservedly recommended to all "individuals and organizations interested in nutritional problems" and especially to all students of clinical hematology.

T. F., Jr.

DEEP ANALYSIS. By CHARLES BERG, M.D. (Lond.), D.P.M. Pp. 254. New York: W. W. Norton, 1947. Price, $3.50.

DEEP ANALYSIS is a brave attempt. However, it falls far short of success. The author does not reveal what moved him to write this book. The jacket "blurb", however, affirms that being dissatisfied with the short case descriptions which abound in psychiatric literature, he undertook to write "a complete Freudian analysis of a single case." The term "complete" is in this instance both tricky and frustrating, for the book is most certainly not complete (*i.e.* fully adequate), either as a case record, or as an exposition of "what goes on" between analyst and patient. Time and again the author writes, as indeed he could not but write, "space will not admit . . . complete exposition;" "space will not permit

a recital of . . ."; "many excellent dreams and their associations will have to be omitted." And toward the end is to be found this frank admission: "Notwithstanding all the care and compendiousness of our transcription of this analysis, as we have not ourselves been able to experience emotionally what the patient under analysis experienced, we remain infinitely short of a true revelation of the daily, hourly, minutely details in all their voluminousness—details which the subject of analysis alone can emotionally experience, and in which alone can lie the appreciation of something as indescribable as life itself" (p. 230).

In this rather long and poorly constructed sentence the author confirms what Freud said more succinctly: "It does not lend itself to demonstration". "One learns it on 'one's own hide' ".

Deep Analysis is a brave attempt, because, even though unsuccessful, it tried to do what to my knowledge no other author has attempted, and that is to reveal the dynamics of treatment and recovery in a given case. That is a much more difficult task than to describe in general terms the *theory* of psychotherapy. To be effective in such an effort the descriptive encompassment would need to embrace the therapist as well as the pathology and the patient. That means that the writer of such a book would have to "get behind" both, the therapist and the patient, and externalize his appreciation of what he does to and with the patient (and vice versa) and why. Most orthodox analysts—and Dr. Berg appears to be strictly orthodox—find such a task difficult, if not impossible. Hence Dr. Berg's confession: "In some of our apparently most successful cases analyst as well as patient are both befogged as to the mechanism which produced results which were beyond their dreams" (p. 229). I. G.

ADVANCES IN BIOLOGICAL AND MEDICAL PHYSICS. Vol. I. Edited by JOHN H. LAWRENCE and J. G. HAMILTON, Division of Medical Physics, Univ. of California. Pp. 484. Illustrated. New York: Academic Press, 1948. Price, $8.60.

THIS text consists of a series of articles on various aspects of radioactivity, written by some of the foremost research workers in the field. Among numerous topics considered are the use of isotypes in clinical and experimental medicine, the physics of radioactivity, results of *in vivo* studies on metabolism with nitrogen and carbon isotopes, instruments used in detection of radioactivity, and recent discoveries made by the use of radioactive phosphorus, iron, and iodine. Also included are chapters devoted to radiation protection, and effects of the atom bomb on the Japanese. Each topic is carefully and thoroughly expounded, and many new developments are described and correlated. I. Z.

AN INTRODUCTION TO MEDICAL MYCOLOGY. By GEORGE M. LEWIS, M.D., and MARY E. HOPPER, M.S., Cornell Univ. 3d edition. Pp. 336; 103 ills. Chicago: Year Book Publishers, 1948. Price, $8.50.

IN LESS than 10 years, this book has gone through 3 editions. Like its predecessors, the first part deals with the clinical, theoretical, and experimental phases of the subject, and the second part outlines pertinent laboratory procedures. This volume is a few pages longer than the second and contains more illustrations. Its format retains the good qualities of the preceding editions; the price, however, is higher. It is suggested that bold face headings would help the reader in locating the material presented and illustrations of the reproductive forms of fungi would help to clarify the later illustrations for the novice.

This is still the most practical volume in English available to the dermatologist who is not a specialist in mycology. H. B.

AN INTRODUCTION TO THE HISTORY OF DENTISTRY. By BERNHARD WOLF WEINBERGER, D.D.S., Prof. of Dental History and Literature, New York College of Dentistry. In 2 vols. Pp. 514 and 408; 177 and 136 ills. St. Louis: C. V. Mosby, 1948. Price, $20.00.

THESE volumes are separate though related works. In the first, Dr. Weinberger considers dentistry from its earliest period to the end of the 18th century. The second is concerned with dentistry in America from 1620 to the middle of the 19th century. Dr. Weinberger's collection of dental bibliographical and historical material is probably the most complete in existence. This and many other sources have been tapped for the numerous reproductions of original title pages, dental advertisements, wood cuts, et cetera, which depict the gradually accumulating knowledge of dental anatomy, physiology, pathology and therapy.

The beginnings of dentistry are lost in the obscurity of prehistoric man. Nevertheless, that dental problems existed is indicated by examination of skulls and teeth which have been recovered by archeologists. Not only are fractured teeth and jaws found but also unerupted and malposed teeth. Caries of the teeth was not so rare among primitive peoples as is commonly reported. The relief of pain from toothache led to the knocking out of teeth and eventually to more refined methods of extraction. The replacement of lost teeth by natural or artificial substitutes was a next step. Gold castings cemented into the teeth were used by South American Indians for

adornment centuries before metals were used for the treatment of dental caries. All this and much more is woven into a background of the history, folklore, medical theory and practice of many races of people down through the Middle Ages to the Renaissance and the beginnings of the biological sciences upon which the practice of modern medicine and dentistry is based. In the final section of the first volume the rise of dentistry as an independent profession and the coincidental growth of dental literature is described.

The development of dentistry in America is documented in greater detail. There are chapters on early dentists including Paul Revere. Other chapters are concerned with George Washington from the point of view of his numerous dental difficulties, and of Charles Wilson Peale, the artist, who was led to the manufacture of porcelain teeth in order to restore a more natural appearance to the face of his distinguished client, Washington. Much material of an incidental historical interest is included.

There are indices of personal names as well as of subject matter. These books are a most valuable contribution to the history of dentistry. P. B.

MIDWIFERY. By TEN TEACHERS, under the direction of CLIFFORD WHITE. 8th ed. Pp. 560; 217 ills. Balt.: Williams & Wilkins, 1948. Price, $6.00.

THIS condensed text has had a well-merited popularity extending over a period of 30 years. Emphasis is placed on the practical side of the subject. Exposition is logically planned and coordinated. The style is uniformly lucid and concise. In this edition, 3 of the original "teachers" have yielded to younger successors. C. B.

THE CLINICAL APPLICATION OF PSYCHOLOGICAL TESTS. By ROY SCHAFER, M.D. Menninger Foundation Monograph Series No. 6. Pp. 346. New York: International Universities Press, 1948. Price, $6.75.

WORKERS in individual adjustment will find much of interest in this Monograph. From the method of presenting the performance on a series of psychological tests by patients suffering from different types of mental illness, rounded pictures of the different pathological syndromes emerge, illustrating characteristic thought and affective processes in each type of illness.

The first third of the book develops diagnostic summaries of 11 pathological states and several sub-classes. The diagnostic summaries, as well as the case studies which constitute the last two-thirds of the book, are based upon the psychological tests now used at the Menninger Foundation.

Ten minutely detailed and 10 more briefly summarized case reports form a valuable addition to the collections of cases already available in the standard works of Klopfer, Beck and Murray.

Mr. Schafer's work is careful and timely. It will be useful both as a reference volume and as a teaching medium. R. C.

NEW BOOKS

A.M.A. Interns' Manual. By THE AMERICAN MEDICAL ASSOCIATION. Pp. 209. Phila.: W. B. Saunders, 1948. Price, $2.25.

Prepared by several of the Councils of the A.M.A., this book is designed to help orient the intern in his hospital duties. There are 9 sections: information relative to internships and residences; clinical and laboratory data; drug administration; useful drugs; treatment of poisoning; diet and nutrition; physical medicine; legal aspects of internship; organization of the American Medical Association. G. R.

The Autobiography of Benjamin Rush, His *Travels Through Life* together with his *Commonplace Book for 1789-1813.* Edited by GEORGE W. CORNER for the American Philosophical Society. Pp. 399; 13 ills. Princeton, N. J.: Princeton Univ. Press, 1948. Price, $6.00.

The "Travels Through Life, an account of sundry incidents . . . written for the use of his children", covers up to 1800, thirteen years before his death. The random notes of the Commonplace Books, or diaries, are equally revealing of this observant, vivid and complex personality. No small part of the value of this careful compilation by a well known writer on medical history is to be found in the Introduction, the 4 Appendices, and the copious footnotes and editorial comments. E. K.

Fundamentals of Psychoanalysis. By FRANZ ALEXANDER, M.D., Clinical Prof. of Psychiatry, Univ. of Illinois. Pp. 312. New York: W. W. Norton, 1948. Price, $3.75.

This book replaces, naturally with many changes, part of the author's "The Medical Value of Psychoanalysis", the 2d edition of which appeared 11 years ago. Its main object is "a comprehensive presentation of fundamental theory and its application to treatment."

The Clinical Management of Varicose Veins. By DAVID WOOLFOLK BARROW, M.D. Pp. 155; 58 ills. New York: Paul B. Hoeber, 1948. Price, $5.00.

On a basis of some 2500 observations on patients or their records, the author builds a dynamic picture of the development of varicose veins, their complications and how they should be treated.

Mineral Nutrition of Plants and Animals. By FRANK A. GILBERT, Ph.D. Pp. 131. Illustrated. Norman: University of Oklahoma Press, 1948. Price, $2.75.

Health Progress, 1936 to 1945. A Supplement to 25 Years of Health Progress. By LOUIS I. DUBLIN, Ph.D. Pp. 147. New York: Metropolitan Life Insurance Company, 1948. No price.

Liver Injury. Transactions of the 7th Conference, January 15, 16, 1948. Pp. 95; 15 ills. Price, $1.50. *Blood Clotting and Allied Problems.* Transactions of the 1st Conference, Feb. 16-17, 1948. Pp. 179. Price, $3.25. *Factors Regulating Blood Pressure.* Transactions of the 2nd Conference, Jan. 8-9, 1948. Frank Fremont-Smith, Medical Director. Pp. 170. Illustrated. New York: Josiah Macy, Jr. Foundation. Price, $2.75.

A Doctor Talks to Teen-Agers. By WILLIAM S. SADLER, M.D., F.A.P.A., Consulting Psychiatrist, Chicago. Pp. 379. St. Louis: C. V. Mosby, 1948. Price, $4.00.

This book, based on the author's experience and "directed personally to young folks", contains considerable information of practical, theoretical and idealistic nature that will be found useful and perhaps inspiring, not only to teen-agers themselves, but to physicians, parents, and others who are concerned with understanding and counselling young people.

W. P.

NEW EDITIONS

Diabetic Manual. By ELLIOTT P. JOSLIN, M.D., Sc.D., Clinical Prof. of Medicine, Emeritus, Harvard Medical School. 8th ed. Pp. 260; 51 ills. Phila.: Lea & Febiger, 1948. Price, $2.50.

Textbook of Anaesthetics. By R. J. MINNITT, M.D., Royal Liverpool United Hospital, and JOHN GILLIES, M.C., Univ. of Edinburgh. 7th ed. Pp. 568; 229 ills. Balt.: Williams & Wilkins, 1948. Price, $8.00.

THIS book continues to increase in size—80 more pages in this edition. New material is presented on the medico-legal aspects of anesthesia, curare and regional anesthesia. There is a good bit of useful information available. R. D.

Control of Pain in Childbirth. By CLIFFORD B. LULL, M.D., and ROBERT A. HINGSON, M.D. Introduction by Norris W. Vaux, M.D. 3d. ed. Pp. 522; 170 figs. Phila.: J. B. Lippincott, 1948. Price, $12.00.

Outline of Histology. By MARGARET M. HOSKINS, Ph.D., and GERRIT BEVELANDER, Ph.D., New York Univ. 2d ed. Pp. 112; 56 ills. St. Louis: C. V. Mosby, 1948. Price, $3.50.

An Introduction to Materia Medica and Pharmacology. By ELSIE E. KRUG, R.N., M.A., and HUGH ALISTER MCGUIGAN, Ph.D., M.D. 5th ed. Pp. 558; 37 ills., 15 color plates. St. Louis: C. V. Mosby, 1948. Price, $4.00.

A useful book especially designed for student nurses.

Organic Chemistry. By ELDIN V. LYNN, Ph.D., Prof. of Chemistry, Massachusetts College of Pharmacy. 3d ed. Pp. 355. Phila.: Lea & Febiger, 1948. Price, $5.00.

Diseases of the Adrenals. By LOUIS J. SOFFER, M.D., Ass't. Clinical Prof. of Medicine, Columbia Univ. 2d ed. Pp. 320; 45 ills., 3 color plates. Phila.: Lea & Febiger, 1948. Price, $6.50.

This book is an interesting and concise monograph, dealing with all aspects of the adrenals but with emphasis on the clinical manifestations of adrenal disease. The new material in this edition includes the clinical and experimental data on pituitary-adrenocortical function which have been accumulated in various medical centers during the last few years. I. Z.

An Introduction to Gastro-Enterology. By WALTER C. ALVAREZ, M.D., Prof. of Medicine, Univ. of Minnesota. 4th ed. Pp. 903; 269 ills. New York: Paul B. Hoeber, 1948. Price, $12.50.

This edition (2d under its new title) represents an improvement over the 3d in that it includes many additions to the sections on intestinal innervation, the functions of the colon and flatulence; also it covers adequately the subjects of electro-enterograms and vagotomy. The text, like that of all Alvarez' writings, is easy to read, and many excellent illustrations are included. The physiological discussions of many gastro-intestinal problems are clear and convincing. An extensive bibliography of about 2800 references adds greatly to its value. It will be found particularly helpful to those investigators in gastroenterology who need a reference guide to the important literature. J. H.

Principles and Practice of Ophthalmic Surgery. By EDMUND B. SPAETH, M.D., Prof. of Ophthalmology, Graduate School of Medicine, Univ. of Penna. 4th ed. Pp. 1044; 649 ills., 8 color plates. Phila.: Lea & Febiger, 1948. Price, $15.00.

THIS first post-war edition of what has already been called in these columns the best book on the subject in the English language contains much new material on, *inter alia*, plastic surgery, plastic enucleation, paralytic squint, exophthalmos, radium therapy and similar subjects. It is 110 pages larger than the 3d edition (1944). Its high standards of breadth of scope and clarity of text, excellent illustrations, and good bookmaking are well maintained.